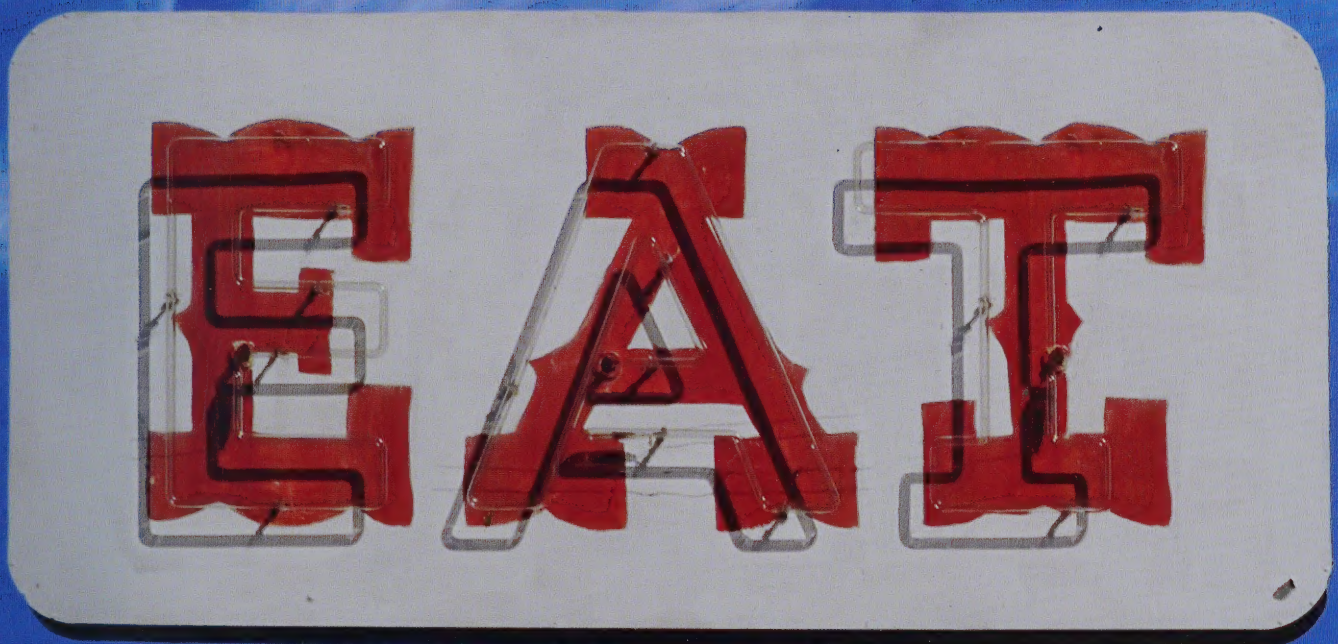
Harvard Medicine

WINTER 2012



Appetite for Life

Harvard scientists probe the complex links between diet and health

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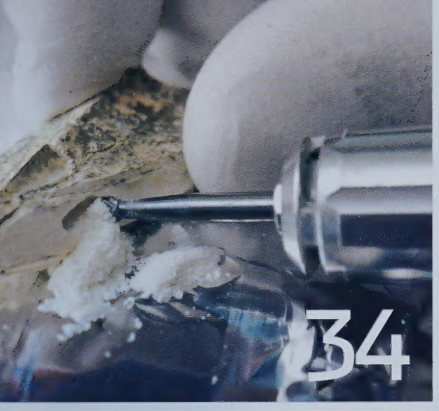
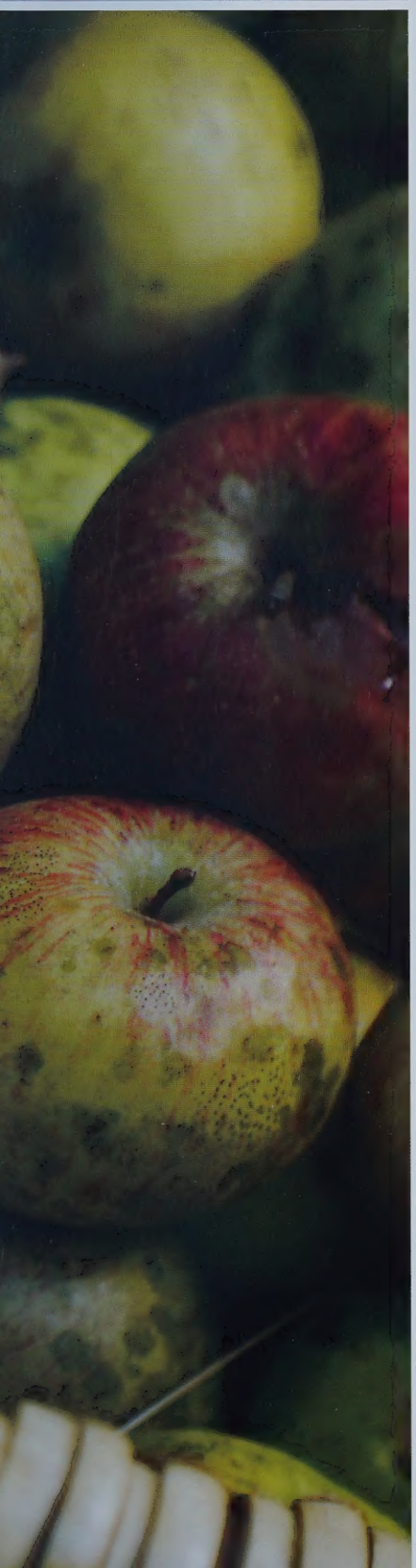
FAMILY HEIRLOOMS: Newtown Pippen, Esopus Spitzenberg, and Roxbury Russet are among the seventeenth- and eighteenth-century apple varieties grown in the orchard of alumnus Eric Chivian.

COVER PHOTO ILLUSTRATION: MATTIAS PALUDI





Special Report: Diet and Health

Features

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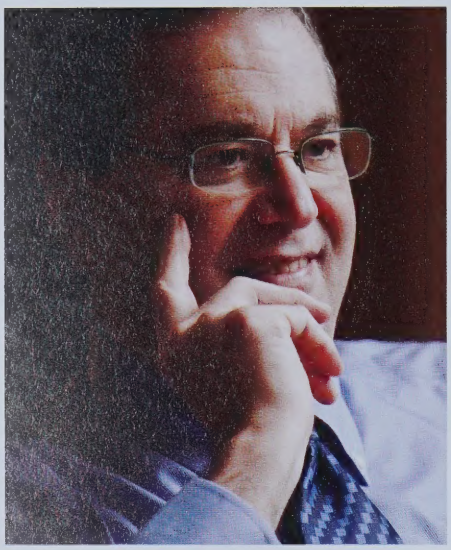
From the Dean

THOUGHTS ON INNOVATION

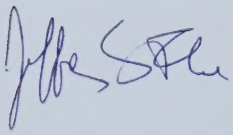


It may well have been a Welsh bard who, wishing to avoid the local physician, sang about the healthy virtues of the lovely apple: late nineteenth-century records trace the proverb to that rugged land. Interest in the saying has not been limited to folklorists. Scientists have parsed the proverb empirically by probing the apple for its healthful merits. A short list of what they've found is worth noting: vitamins A, C, and E; pectin, to lower blood pressure; quercetin, to reduce cancer risk, and boron, to build bone. The proverb, it seems, holds at least a few seeds of truth.

While this issue of *Harvard Medicine* isn't an ode to the apple, it does draw inspiration from its image. And what better for an issue on diet and health? Within these pages, you can read about how science is carefully dicing the data on associations between diet and disease, eating and aging, and even peanuts and therapeutic success. You will also find how research is clarifying those associations using the power of reports from multiyear epidemiological studies and the nuance offered by controlled laboratory investigation. The role of nutrition in healing has not been overlooked either, as you can read about how the critically ill were served in the past and how they are sustained today.

If you wish to clear your palate of analyses, you might explore the beauty of biodiversity and the joy of using the fruits of the garden prescriptively. And for those who enjoy a mystery, this issue tells two, one a tale that begins in Siberia and ends with a new branch of our family tree, and another that describes the search for a vaccine against HIV—a story without resolution, but not, you will find, without progress or hope.

Perhaps science will one day certify apples as our best medicine. But until that day, we can take guidance—and heart—from what research is revealing about diet, disease, and well-being, and, using that knowledge as our guide, recognize food for what it truly is, an indispensable path to lifelong health.



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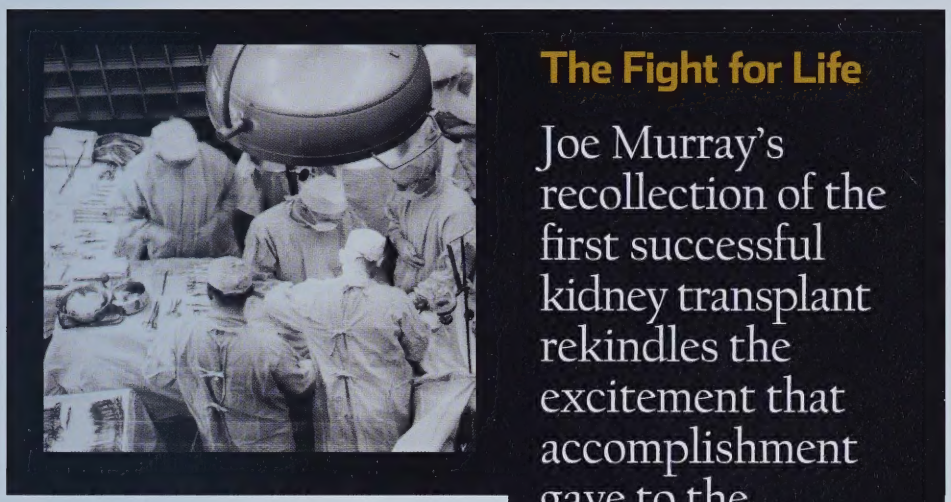
Letters to the Editor

SECOND OPINIONS FROM OUR READERS



The Fight for Life

Joe Murray's recollection of the first successful kidney transplant rekindles the excitement that accomplishment gave to the worldwide medical community.

ANTHONY PATTON '58
DANVERS, MASSACHUSETTS

Sweet Sorrow

I loved The Science of Emotion issue (Summer 2011). In real life, of course, emotions are more complex than our simple taxonomies of fear-anger-love-sadness, so it is not surprising that the boy whose picture opens the article on anger shows more than wrath. Anger brings the eyebrows down, but this boy's brows go up; they are knitted together, his cheeks are raised, and his lips stretch in a way that can also signal pain. That's appropriate for those of us who know we're reading the last issue from *Harvard Medicine*'s longtime editor, Paula Byron. So many of the best story ideas, issue themes, and more outrageous headline puns have come from Paula. She was consistently able to feature the work of many of the great writers from among the alumni because of her fresh intelligence and her ability to make the magazine so much more than an ordinary alumni rag. It hurts to see her go.

ALICE FLAHERTY '94
BOSTON, MASSACHUSETTS

To Listen, To Learn

Joe Murray's recollection in the Summer issue of *Harvard Medicine* of the first successful kidney transplant rekindles the excitement that accomplishment gave to the worldwide medical community. That year, 1954, was my first at HMS. To me and to many others, surgery seemed to be poised to solve many great health problems, including cancer, heart disease, and organ transplantation. Many of us tried to join the effort and chose surgery as our careers. Surgery seemed exciting and creative, and it beckoned us to participate. Indeed, some of those expectations bore fruit: Heart surgery became routine and transplantation successes increased.

But the lesson of Joe Murray's success lies in the willingness of that surgical team to learn, share, and cooperate. These men were experts on the scientific issues of transplantation but, true to their roles as good clinicians, they were willing to listen to the insight of David Miller, the referring local doctor who suspected that a transplant could work between identical twins.

While we should never disparage the insights from a computer's analysis of data or the measurable results from a well-crafted experimental protocol, it benefits us to remember that significant discoveries can come from the bedside questions and observations of clinicians. In our daily work as doctors, sooner or later, there will be the patient who defies the odds, whose cancer stops growing or disappears with little or no treatment, whose heart failure improves beyond therapeutic reason, or whose terminal artery disease is alleviated by massive collaterals. Perhaps another discovery awaits in our waiting room—or in the emergency call that will come at 3:00 a.m.

So Joe Murray saved a life—and made history—because he had the courage to consider David Miller's idea that a kidney could perhaps be transplanted successfully between identical twins. That spot in history, and the Nobel Prize that commemorates it, could not have happened to a more deserving gentleman or surgeon.

ANTHONY PATTON '58
DANVERS, MASSACHUSETTS

Glass Half Full

The Class Notes in the Summer issue of *Harvard Medicine* stated that I directed the International Centre for Diarrhoeal Diseases Research in Bangladesh from 1979 to 1982. I actually had the privilege of directing that center through 1985—a trivial change. But I would like to share a not-so-trivial point about the Centre and its progenitor, the Cholera Research Laboratory.

These institutions gave birth to oral rehydration therapy, an intervention that annually saves the lives of nearly 6 million children throughout the world. Much of the science on which this therapy was founded grew out of work on carrier-mediated transport from the Harvard Biophysics Research Laboratory in the late 1950s and early 1960s. This is perhaps one of the better examples of the translation of basic research into a highly effective and inexpensive therapy that does not require doctors, nurses, or health workers to administer it.

WILLIAM B. GREENOUGH III '57
BALTIMORE, MARYLAND

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*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, Massachusetts 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity. The magazine also welcomes ongoing feedback through its Readers' Panel. To become a member, visit harvardmedicine.hms.harvard.edu/feedback.php.*

OUT WITH THE OLD: The new Initiative in Systems Pharmacology will explore how drugs work in complex living systems with the goal of making drug discovery and development faster, cheaper, and more effective.

All Systems Go

Initiative will spur development of effective drugs

TAKING AIM at the alarming slowdown in the development of new and lifesaving drugs, HMS is launching the Initiative in Systems Pharmacology, a comprehensive strategy to transform drug discovery by convening biologists, chemists, pharmacologists, physicists, computer scientists, and clinicians to explore together how drugs work in complex systems.

Modern drug discovery has focused on the interaction between a candidate drug and its immediate cellular target. That target is part of a vast and complex biological network, but because studying the drug in the context of a living system is profoundly difficult, scientists have largely avoided this approach.

"Our inability to develop a coherent picture has stymied drug discovery for a long time," says Marc Kirschner, the John Franklin Enders University Professor of Systems Biology and chair of the HMS Department of Systems Biology. "It's as if we have a map of a highway system that contains only small pieces extending a few miles here and there, without any connectivity on a large scale."

A better understanding of the system of biological molecules that controls medically important biological behavior, and the effects of drugs on that system, will help industry identify the best drug targets and biomarkers. This will help to identify the most promising drug candidates earlier, ultimately making drug discovery and development faster, cheaper, and more effective.

Led by Kirschner and systems biology professors Peter Sorger and Tim Mitchison, the initiative will apply the innovative approaches of systems biology, which analyzes specific biological processes within the context of an entire living system, to the understanding and prediction of drug activity. In addition to its research component, the effort will include an educational program to train future leaders in systems pharmacology and therapeutic discovery. —*R. Alan Leo*

PODCAST

From Crisis to Cures: Writing a New Prescription for Drug Development
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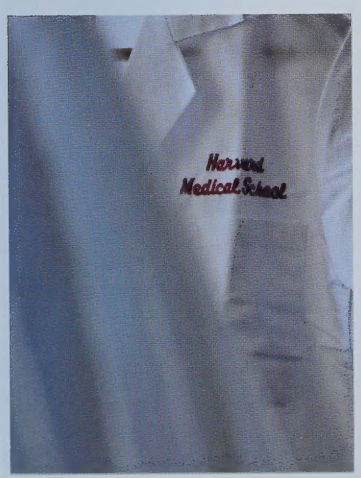
NEXT UP

The Class of 2015 debuts

THE WHITE COAT ceremony made it official: On August 16, 2011, the 165 students in the Class of 2015 slipped on the short coat, a beacon of their professional pursuit. This newest group of HMS students includes graduates of 66 colleges and universities who hail from 33 states, as well as the District of Columbia, Puerto Rico, and seven other countries—Canada, China, France, Ghana, India, Korea, and Togo. The students range in age from 20 to 30, with 62 percent having majored in biology, chemistry, math, or engineering as undergraduates. Men make up 53 percent of the class; 34 percent is Asian or Asian American, and 19 percent is African American, Cuban, Hispanic, Mexican American, Native American, Native Hawaiian, or Puerto Rican. Although 42 percent entered directly from undergraduate programs, 26 percent graduated one year previous, and 32 percent graduated two or more years earlier. *—Susan Karcz*



FIRST IN CLASS: Helen Shields is the first faculty member to be promoted within a newly defined classification of teaching and educational leadership, a revision to advancement categories brought about by a review of the promotions process.

Title Match

Revised criteria expand promotion categories

HER PAGER BEEPED as she was in a lecture hall at Beth Israel Deaconess Medical Center, waiting to teach a course in December 2010. Looking down, Helen Shields recognized the number as one she had been hoping to see, and anxiously stepped back into the hallway. The gastric bypass surgery case discussion would have to wait. Hands fumbling with excitement, Shields answered the page and discovered she had been named a full professor of medicine at HMS.

Shields, in fact, had become the first faculty member to be promoted within the newly defined classification of teaching and educational leadership. This classification was created in 2008 as part of revisions to the promotions process recommended by a task force report issued by HMS Dean Jeffrey Flier. Although promotion decisions had previously been based on two classifications, investigator and clinician teacher, the task force recommended that the criteria be broadened to reflect faculty members' varied areas of achievement. These now include excellence in academic achievement and contributions to teaching and education.

"For the past three years, Harvard Medical School has been looking very closely at the way we evaluate faculty for promotion at all levels," says Maureen Connelly, dean for faculty affairs at HMS. "Although our evaluation of our promotion mechanisms remains an ongoing assessment, we have made strides. And we are already seeing the fruits of that progress."

Shields's promotion stands as proof. "The process for my promotion was like an open door," she says, "an open forum for discussion. I felt valued and supported every step of the way."

Building on the task force's recommendations, the Office for Faculty Affairs has been instituting mechanisms to streamline faculty promotions. For example, parts of the process that had previously occurred at the hospital level are now consolidated at HMS. In addition, the Dean's Office, the academic departments, and the affiliates work more collaboratively to ensure a fair and efficient review. These revisions are expected to collapse the time it takes for a candidate to be promoted to professor to less than one year in the majority of cases.

The streamlining has been fully phased in, and all departments are now using the new system. The first candidates to go through the expedited process could receive word of their promotion status by the beginning of 2012.

In 2010, there were 96 promotions to full professor. "We've accelerated the pace of promotions without compromising the rigor of the review," Connelly says.

Shields, for one, is satisfied with the changes. "I felt an amazing sense of fulfillment and happiness." *—Katie DuBoff*

PHOTOS: LEN RUBENSTEIN (RIGHT); JOHN SOARES

KEEN EDGE

Cognitive abilities do not inevitably dim with age

AGE DOES NOT AUTOMATICALLY BRING cognitive decline, according to research reported in the November 2011 issue of *Age and Ageing*. The research, by scientists at the Institute for Aging Research of Hebrew SeniorLife, together with colleagues at Duke and Rush Universities, indicates, in fact, that two out of every three older adults experience only a trivial amount of decline in cognitive performance over late-life decades. The findings challenge widely held beliefs about cognitive decline and aging.

Institute researchers analyzed data from a large study involving more than 1,000 adults 56 to 102 years of age. Study participants were followed for up to 15 years and their cognitive performance was measured annually.

Using those data, the researchers classified participants as having slow, moderate, or rapid cognitive decline. Cognitive scores were determined by a scoring system that differed from, but can be compared with, IQ scoring: If 100 is average, the normal range falls between 70 and 130. For participants in the slow-decline group, this would mean that between ages 75 and 90, their cognitive score would be expected to dip from 100 to 94. For participants in the moderate-decline group, their cognitive score would be expected to change from 100 to 75 over the same age span, while participants experiencing rapid decline would be expected to move from 100 to 57 during those 15 years.

The findings carry implications for the care of seniors. Currently, cognitive decline is assumed to be a part of normal aging, which can lead to clinicians translating poor mental performance by elderly patients as something to be expected. With the knowledge that such decline is not a given, say the researchers, poor performance can be investigated, and preventable or reversible conditions, such as delirium, medication side effects, or vitamin deficiency, can be properly addressed. *—Scott P. Edwards*

Back Spin

Imaging technique shows progress of pain

A PICTURE SOON MAY BE WORTH more than a thousand words to those who suffer chronic low-back pain. Researchers at Brigham and Women's Hospital, using arterial spin labeling, a new imaging technique, have been able to follow the changes in brain activity that occur when chronic low-back pain worsens. The research, published in the August 2011 issue of *Anesthesiology*, may one day provide physicians with a much-needed objective measure of pain progression among those who endure chronic discomfort.

"This study provides tools to objectively describe a subjective experience, that of chronic pain," says lead author Ajay Wasan, an HMS assistant professor of psychiatry at the Pain Management Center at Brigham and Women's. "When a patient's pain worsens, we found there are changes in activity in the areas of the brain that process pain and mood."

Working with 16 patients with chronic low-back pain and 16 healthy volunteers, researchers determined participants' pain baselines, had them perform clinical maneuvers such as pelvic tilts to exacerbate pain, then applied heat to their skin to match the pain experienced during movement. During the movement and heat sessions, researchers used arterial spin labeling imaging, which allowed them to quantify the blood flow, and, thus, neuronal activity, to specific regions of the brain over time.

They found that, for those suffering from chronic pain, brain activity increased in response to the pain-spiking movements but not to the heat-induced pain. Healthy participants showed no activity increases. The researchers hope the work will lead to a better understanding of neurocircuitry at the individual level and, ultimately, the development of personalized therapies.

CALL TO ORDER: Scientists have discovered that, within healthy cells, single chains of the alpha-synuclein protein cluster to form four-chain units that twine together in an orderly fashion.

Figure Study

Findings upend thinking on shape of pivotal protein

WHEN IT COMES TO PROTEINS, function follows form. Each twist and turn in the chain of amino acids making up a protein contributes to its unique properties and behavior, so it's critical for scientists to accurately describe the arrangement of folds. But sometimes, they get the entire pattern wrong.

Consider, for example, alpha-synuclein, a protein integral to Parkinson's disease. Scientists have long thought the protein occurs in healthy cells as a single randomly coiled chain that resembles a writhing snake. Yet an innovative approach has shown that it has a radically different shape in healthy cells than previously thought. Writing in the September 1, 2011, issue of *Nature*, a research team led by Dennis Selkoe, the Vincent and Stella Coates Professor of Neurologic Diseases at Brigham and Women's Hospital and Harvard Medical School, reports that the protein's structure is orderly and sophisticated. This finding challenges existing disease paradigms and could suggest a new therapeutic approach.

Selkoe's team began its investigation by asking whether techniques used to probe the protein's clustering behavior might be overlooking important aspects of the protein's natural biology. So they designed new experiments to probe alpha-synuclein's behavior.

The initial data took them by surprise. There were no single isolated chains of alpha-synuclein. Instead, the data suggested that cells package four alpha-synuclein chains together as a tetrameric unit. The team confirmed this finding, showing that the unit consists of alpha-synuclein chains that have orderly twists.

In addition to providing new lines of therapeutic inquiry, the discovery of the folded tetramers should help labs shed light on the function of alpha-synuclein in healthy cells. —*Alyssa Kneller*

VIDEO EXTRA

New Clue to Parkinson's: Shape of Key Protein Surprises Researchers
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CHAIN SMOKING

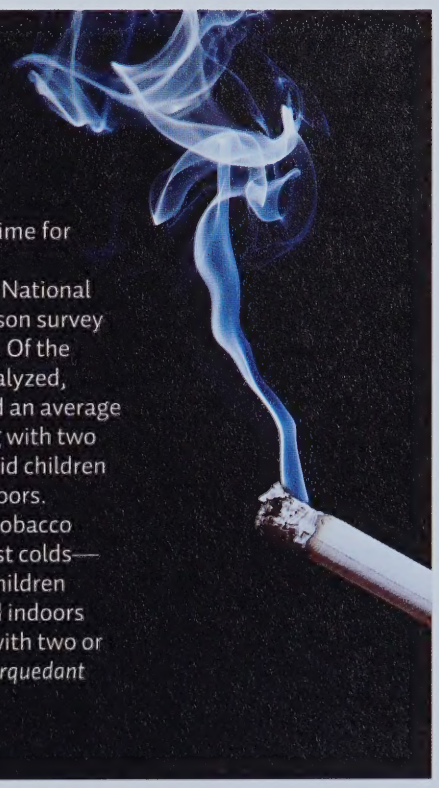
Smoke exposure at home increases illness-related school absences

CHILDREN WHO ARE EXPOSED to tobacco smoke at home miss more days of school than do children living in smoke-free homes, says a report from investigators at Massachusetts General Hospital. The researchers also find these children have higher rates of respiratory illnesses that can be caused by second-hand smoke. The study appears in the October 2011 issue of *Pediatrics*.

"Among children ages 6 to 11 who live with smokers, one-quarter to one-third of school absences are due to exposure to smoke in the household," says lead author Douglas Levy, an HMS assistant professor of medicine and a member of the faculty at the hospital's Mongan Institute for Health Policy. "On a national basis, these absences result in $227 million in lost wages and time for caregivers or their employers."

The team analyzed data from the 2005 National Health Interview Study, an annual in-person survey of representative households nationwide. Of the 3,087 children whose information was analyzed, those living with one in-home smoker had an average of 1.06 more days absent, and those living with two or more had 1.54 more days absent than did children living in homes where no one smoked indoors.

Illnesses associated with exposure to tobacco smoke—including ear infections and chest colds—accounted for 24 percent of absences in children living in homes where one person smoked indoors and 34 percent for those living in homes with two or more in-home smokers. —*Katie Marquedant*



HORIZONTAL PRESSURE

Poor sleep quality increases risk of high blood pressure

THE QUALITY OF SLOW-WAVE SLEEP, a deep stage of sleep from which it is difficult to awaken, is a powerful predictor of high blood pressure among older men, say researchers at Brigham and Women's Hospital, together with colleagues at the University of California, San Diego. In research published in the October 2011 issue of *Hypertension*, scientists report that participants who spent less than 4 percent of their sleep time in slow-wave sleep, a percentage determined by measuring sleep durations and tallying the number of awakenings during the night, had an 80-percent increased risk for developing hypertension. In addition, the investigators found that this heightened risk was independent of the influence of breathing pauses during sleep, a condition known as sleep apnea. Study author Susan Redline, the Peter C. Farrell Professor of Sleep Medicine at HMS and Brigham and Women's, noted that although women were not included in this study, "those who have lower levels of slow-wave sleep may also have an increased risk of developing hypertension."

NETWORK NEWS: Detailed plot of interactions between proteins in fruit fly cells offers insight into function.

Map Quest

Protein-interaction schema is largest one yet for multicellular organisms

RESEARCHERS HAVE BUILT A MAP that shows how thousands of proteins in a fruit fly cell communicate with each other. This is the largest and most detailed protein-interaction map of a multicellular organism, demonstrating how approximately 5,000, or one-third, of the proteins cooperate to keep life going.

"My group has been working for decades, trying to unravel the precise connections among the proteins and gain insight into how the cell functions as a whole," says Spyros Artavanis-Tsakonas, an HMS professor of cell biology and senior author on the paper, published October 28, 2011, in *Cell*. "For me, this map is a dream come true."

Humans and fruit flies are descended from a common ancestor, and in most cases, both species rely on the same ancient cellular machinery for survival. Despite the huge amount already known about the fruit fly and its genes, much about the function of its thousands of proteins remains a mystery. This map now gives precise clues to their function, offering scientists important insights into the process of development as well as a useful guide to the cellular activity of many higher organisms.

VIDEO EXTRA

Fly Paper: Mapping the Protein Interactions of Our Distant Relative
harvardmedicine.hms.harvard.edu

"This is of extraordinary translational value," Artavanis-Tsakonas says. "In order to know how the proteins work you must know 'who' they talk to. And then you can examine whether disease somehow alters this conversation." —*Robert Cooke*

IMAGES: ZEPHYR/SCIENCE PHOTO LIBRARY (FAR LEFT); COURTESY OF ARTAVANIS-TSAKONAS LAB

A GENTLE AWAKENING

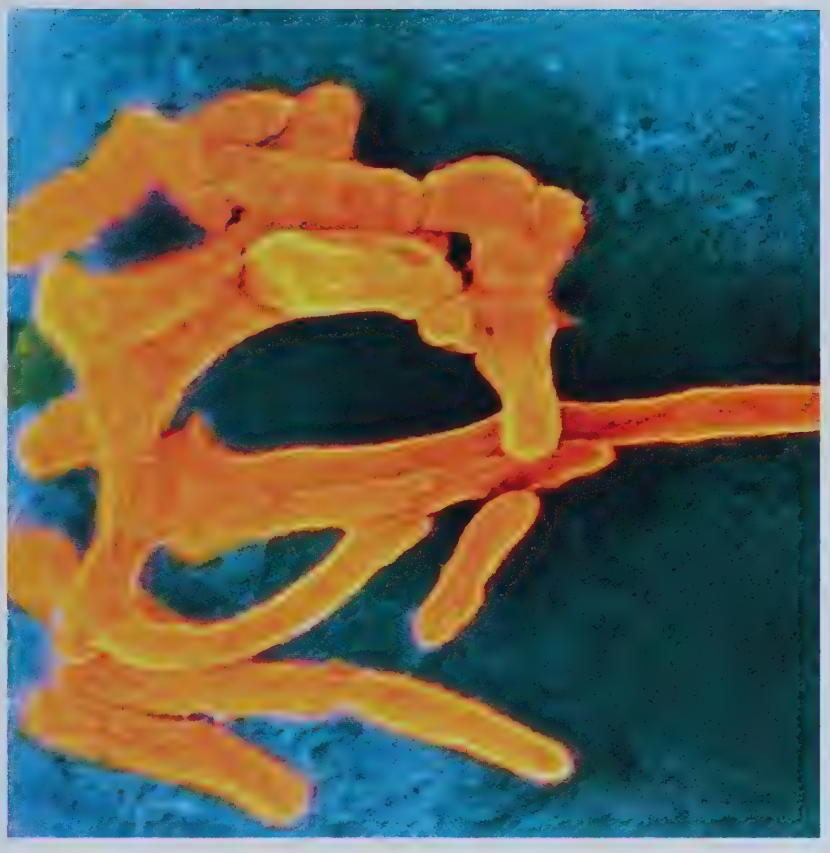
Common stimulant may speed recovery from general anesthesia

THE COMMONLY USED STIMULANT drug methylphenidate, more often referred to as Ritalin, may be of use in the operating room, according to a study in animals conducted at Massachusetts General Hospital. The report, appearing in the October 2011 issue of *Anesthesiology*, is the first demonstration in mammals of what could be a safe and effective way to induce arousal from general anesthesia.

"If these findings can be replicated in humans," says Emery Brown '87, senior author of the paper, and the Warren M. Zapol Professor of Anaesthesia at Harvard Medical School and Mass General, "it could change the practice of anesthesiology by potentially reducing post-anesthesia complications like delirium and cognitive dysfunction in pediatric and elderly patients."

Methylphenidate is widely used to treat attention-deficit hyperactivity disorder and is known to affect arousal-associated pathways controlled by the neurotransmitters dopamine, norepinephrine, and histamine. The current study showed that the drug stimulated arousal in rats receiving an anesthetic and, if administered before halting anesthesia, prompted a faster recovery than that shown in rats receiving a saline injection. According to the investigators, more precise ways to induce and control the arousal process may lead to strategies that help patients recover from coma. And the ability to safely reduce the time patients spend in the operating room could translate into significant savings in health costs. —*Sue McGreevey*

PHOTOS: LEN RUBENSTEIN (RIGHT); UNKNOWN PHOTO LIBRARY



Keeping an Eye on the Neighbors

Bacterium may play a role in colorectal cancers

AN ENTICING CLUE to a possible cause of colorectal cancer has been discovered by researchers at Dana–Farber Cancer Institute and the Broad Institute of MIT and Harvard. The research team, writing in the October 18, 2011, online issue of *Genome Research*, reports finding a strikingly large number of *Fusobacterium* cells in nine colorectal tumor samples. If the bacterium is implicated in colorectal cancer, it could be useful in diagnosing, preventing, and treating the disease.

A confirmed connection between *Fusobacterium* and the onset of colorectal cancer would mark the first time any microorganism has been found to play a role in this type of cancer, which is the second leading cause of cancer deaths in the United States.

The discovery was made by sequencing the DNA within nine samples of normal colon tissue and nine of colorectal cancer tissue, and validated by sequencing 95 paired DNA samples from normal colon tissue and cancerous colon tissue. Analysis of the data showed large amounts of *Fusobacterium* DNA in the tumor tissue.

Throughout the past decade, there has been an increasing focus on the relationship between cancer cells and their "microenvironments," specifically on the cell-to-cell interactions that may promote cancer formation and growth. While the relationship, if any, between colorectal cancer and *Fusobacterium* is unclear, there are intriguing hints that the bacterium may play a role in the cancer, says senior author Matthew Meyerson '89, an HMS professor of pathology and codirector of the Center for Cancer Genome Discovery at Dana–Farber.

"It may be that the bacterium is essential for cancer growth, or that cancer simply provides a hospitable environment for the bacterium," Meyerson observes. Researchers are now studying *Fusobacterium* levels in larger numbers of patients with colorectal cancer and in those without the disease.


B2
B3
B4
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C2
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PLATE SHIFTS

When choosing what to eat, it's best to go green BY JESSICA CERRETANI

PHOTOS: RUBBERBALL PRODUCTIONS/GETTY IMAGES (LEFT AND PREVIOUS SPREAD)

Kate feels like she's tried everything: Weight Watchers, Jenny Craig, grueling workouts at the gym. Yet she could swear those extra 50 pounds remain, stubbornly stuck to her hips. When she confesses her exasperation during her annual physical, her physician makes an intriguing suggestion: Allow him to take a blood sample. Although she's pretty sure that obesity is obvious without a test, she goes along with her doctor's request.

The results are stunning. Kate's blood reveals a genetic sensitivity to carbohydrates, explaining in part why she doesn't respond well to low-fat diets, which tend to be abundant in such refined carbs as pasta and rice. With this knowledge, her physician tailors a diet to work with her individual biochemistry, greatly increasing the odds that she'll shed those pounds—and keep them off.

Although this sounds like yet another weight-loss gimmick—or a scene out of Woody Allen's *Sleeper*—it is a scenario grounded in hard science. A growing body of nutrition research suggests that a personalized diet based on a patient's genetic makeup will someday become reality, making the prescription for good nutrition and weight loss as close as a visit to the doctor's office.

"There's a lot of excitement in research circles about the concept of dietary phenotypes, or the way our genes interact with food," says David Ludwig, an HMS professor of pediatrics and director of the New Balance Foundation Obesity Prevention Center at Children's Hospital Boston. In a study published in 2007 in the *Journal of the American Medical Association* and reported heavily in the media, Ludwig and his colleagues tested insulin response in a group of 73 obese young adults before giving them either a high-carb, low-fat meal or a low-glycemic meal rich in non-starchy vegetables and legumes. Glycemic measures, often expressed along an index as low, medium, and high, refer to how quickly foods break down and release glucose during digestion. The researchers found that people who tended to secrete high levels of insulin after ingesting glucose, compared with levels secreted by their peers, were more likely to lose weight when they followed a low-glycemic diet than when they adhered to a low-fat diet, probably because they were more sensitive to refined carbohydrates.

These results, says Ludwig, could explain individual differences in the ability to lose weight. "When it comes to food," he adds, "one size doesn't necessarily fit all." Eventually, this knowledge could help physicians learn which patients will respond best to which types of diets—all determined by a simple blood test measuring insulin secretion.

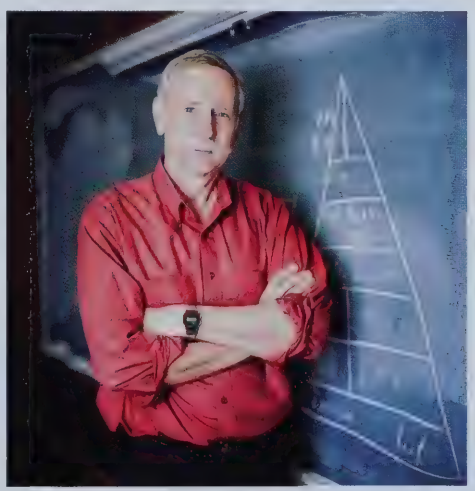

PHOTO COURTESY OF LOOKING LIGHT

SECRETS OF THE PYRAMID: Using data from large epidemiological studies, Walter Willett teases out the links between diet and disease.

Food for Thought

Patients like our fictional Kate aren't alone in their struggles with the scale. Recent findings by researchers at the Harvard School of Public Health and elsewhere suggest that billions of people are fighting—and losing—the battle of the bulge. Worldwide, an estimated 1 in 3 adults is overweight and 1 in 9 is obese, according to a study published in February 2011 in *The Lancet*. The number of obese people now tops half a billion—a doubling of prevalence in less than three decades. And extra pounds don't just present a threat to our self-esteem. The World Health Organization estimates that obesity-related illnesses, including cardiovascular disease and stroke, type 2 diabetes, and cancers of the breast, endometrium, gallbladder, kidney, colon, and esophagus, claim some 3 million lives each year. Statistics like these are helping to spur investigations into the potential causes of obesity and related diseases—starting with what we put on our plates.

"Research in the 1950s and '60s first suggested a connection between food and the development of chronic conditions such as heart disease," says Walter Willett, an HMS professor of medicine and chair of the Harvard School of Public Health's Department of Nutrition. "Today, we're continuing to discover that many illnesses may be linked to modifiable risk factors like diet."

The key to establishing clear and accurate dietary advice may lie in the type of studies investigators conduct. Willett has been a driving force behind some of the largest epidemiological studies on nutrition, including the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study. These three studies have identified strong relationships between nutrition and disease, including links between the consumption of red meat and an increased risk of colorectal cancer; consumption of alcohol and an increased risk of breast cancer; and consumption of partially hydrogenated fats (also known as trans fats) and an increased risk of cardiovascular disease—data that have helped form much of our current dietary advice and guidelines.

Systematic reviews, in which investigators analyze studies to tease out and compare the similarities and differences in their results, and meta-analyses can provide even more insight into food and disease risk. "One study is never enough to make or break a key finding," says Eric Ding, an HMS instructor in medicine at Brigham and Women's Hospital. Ding also is affiliated with the Department of Nutrition at the Harvard School of Public Health. "Research has to be replicated time and again to show a solid relationship between nutrition and health."

"Different studies may look at the effects of nutrition in varied populations with a range of backgrounds and risk factors," explains Ding. "Systematic reviews can help account for variations in findings among studies." Such reviews can also aid investigators in pinpointing specific relationships between food and disease so that umbrella statements about benefit and risk gain precision.

Lean Cuisine

Nutrition research can also overturn misconceptions about diet and health. "There are a lot of strong beliefs in the area of nutrition—it's not unlike religion," says Willett. "The trouble is that the strength of these beliefs often seems to be inversely related to the strength of the data." He points to long-held convictions that eggs are major culprits in cardiovascular disease and that margarine is a healthy alternative to butter. We now know that egg consumption has no real association with heart attacks and that the trans fats found in processed foods, and earlier formulations of margarine, are far worse for cardiovascular health than the saturated fat in butter. Yet this sea change in dietary guidance came only after several decades of research by Willett and scientists at other institutions.

Today, as studies continue to shed light on the most promising foods for good health, one significant theme has emerged: While caloric intake still governs weight gain and loss, *what* we eat may matter just as much as *how much* we eat. Ludwig and his colleagues share some responsibility for this shift in thinking. In 1999, curious to better determine how dietary composition affected body-weight regulation, Ludwig's research team gave 12 obese teenage boys a meal that ranked low, medium, or high on the glycemic index. Each of the meals had the same number of calories, only the foods varied. The meal that registered high on the glycemic-index scale consisted of instant oatmeal, a refined carbohydrate; the medium-indexed meal featured steel-cut oatmeal, a more complex carbohydrate, and the meal low on the glycemic-index scale included an omelet, rich in protein and fat.

The result: blood sugar spiked after instant oatmeal, only to crash a few hours later, leaving the boys much hungrier—and leading them to consume about 700 more calories—than their peers who dined on steel-cut oatmeal or an omelet. "The findings suggested that meals with a high glycemic index provoke hormonal and metabolic changes that trigger overeating," says Ludwig. "We've spent the past 12 years or so refining our research of this concept."

Studies by Eleftheria Maratos-Flier, an HMS professor of medicine at Beth Israel Deaconess Medical Center, suggest that diet composition has an impact on weight gain and weight loss. Diets high in carbohydrates and fats can pack on the pounds, while those

SCALABLE OPTIONS: Eleftheria Maratos-Flier (right), David Ludwig, and C. Ronald Kahn all investigate how macro- and micronutrients affect wakefulness and well-being.

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low in sugar and in total carbohydrate may help spur weight loss. In a study published in the June 2007 issue of the American Journal of Physiology, Endocrinology, and Metabolism, Maratos-Flier and colleagues fed mice one of four diets: high-sugar, high-fat, restricted calorie; very-low-carbohydrate, high-fat; or regular chow. While the mice on the high-sugar, high-fat diet became obese, those on the very-low-carbohydrate, high-fat diet lost as much weight as those whose calories were restricted—even though they consumed as many calories as the mice fed the high-sugar, high-fat diet.

Looking more closely, her team identified biochemical processes behind such findings. They found that the very-low-carbohydrate, high-fat diet appeared to stimulate the production of fibroblast growth factor 21, a liver-derived protein that triggers the body to burn fat. Although the effect of low-carbohydrate diets on FGF21 in humans is less clear, Maratos-Flier remains optimistic—and believes such an eating plan may be the key to weight loss for some people. "A successful diet is a successful diet," she says. "If someone is having trouble losing weight, it's worth a shot to restrict carbohydrates."

Fare Trade

Before you switch your cereal for steak, though, consider this: "The quality of macronutrients that we eat is tremendously important for good health," says Willett. Take fat, for instance. On the whole, it isn't always bad—the monounsaturated fat in such foods as olive oil and nuts, the polyunsaturated fats in vegetable oils, and the omega-3 fats found in fish like salmon and sardines have all been shown to have cardiovascular benefits.

Likewise, all carbohydrates are not created equal. "Some carbs may be just as problematic for cardiovascular health as saturated fat," says Ding. Those that rank high on the glycemic index can cause blood sugar levels, and then insulin production, to skyrocket, which can lead to decreases in HDL ("good") cholesterol and higher levels of triglycerides—both of which can raise cardiovascular risk. Carbohydrates near the top of the glycemic index have also been linked to a greater risk of type 2 diabetes. Over time, the spikes in insulin production that these foods trigger can fatigue the pancreas, so that it stops producing sufficient quantities of the hormone. The inevitable crash in blood sugar levels that follows consumption of these carbohydrates can result in weight gain, too, as the drop tends to spark a feeling of hunger, increasing the likelihood of overeating and, perhaps, increasing the odds of developing heart disease and diabetes.

Although it may seem clear that we should all try to avoid white bread, candy bars, and other carbohydrate culprits that top the glycemic index, troublesome carbohydrates can lurk in less expected places. Potatoes, especially their baked and mashed forms, Ding notes, rate quite high on the glycemic index—they've been shown to raise blood sugar levels as quickly as pure table sugar does—yet their inclusion in the produce food group can cause people to think of French fries as a vegetable rather than a starch.

High amounts of sugar and high-glycemic index carbohydrates work in more insidious ways. "Over the past several years," says Willett, "we've come to see that sugar-sweetened beverages are a very troubling part of the food supply." Observational studies have linked soft drinks and other sugary beverages to excess weight gain, an association that Willett attributes partly to the drinks' carbohydrate content but also to their form. "It's easier, he says, to consume more calories

when they're delivered in a liquid. Ding agrees. "If you eat a handful of jellybeans, you know you're having a snack that's high in sugar and calories," he explains. "But you could drink several sweetened beverages and not realize just how much you're taking in—plus, they're not filling, so you may find yourself snacking in addition to drinking."

Although more randomized, controlled trials are needed to firmly establish this relationship, some research suggests that cutting back on sugary drinks may encourage weight loss. Ludwig's pilot study of 103 adolescents, published in 2006 in *Pediatrics*, found that reducing intake of sugary drinks among adolescents who were overweight—that is, having a body mass index (BMI) greater than 25 kg/m^2—led to a 0.75 kg/m^2 decrease in BMI over a 25-week period, when compared with a control group. For a 160-pound, 5'6" adolescent, this roughly translates to an 11-pound weight loss over the study period.

Vegging Out

If there's one area of nutrition research where findings seem clear-cut, it's fruits and vegetables. Mom always told us to eat our broccoli, and her advice has been backed up by the U.S. Department of Agriculture's recommendations to fill our plates with five to nine daily servings of produce. Whether you meet this requirement or not, you likely have heard that fruits and vegetables have powerful anticancer properties.

There's just one problem. "The benefits of produce for cancer prevention have been greatly overstated," says Willett. Although early case-control studies suggested that fruits and vegetables might protect against cancer, those studies relied on research participants' recollection of their diet, a methodology notorious for recall bias. More recently, large prospective studies have examined the role of produce in overall cancer risk, with disappointing results. (To highlight the complexity of such research, Willett points out that these same studies have shown produce's benefits for cardiovascular disease.) Summing up these findings in a report in the April 21, 2000, issue of the *Journal of the National Cancer Institute*, Willett wrote that evidence to date suggests that "a broad effort to increase consumption of fruits and vegetables will not have a major effect on cancer incidence."

So should you toss that salad? Not so fast, say researchers. First, cancer itself can pose a challenge to investigators. "There are so many different types and subtypes," explains Ding. Some research has identified specific compounds within foods that may indeed help reduce the risk of certain cancers. "Additionally, most cancers have their roots in young adulthood or even earlier, yet the majority of studies have focused on middle-aged and older people," he adds. "We need to start tracking cancer throughout life to get a clearer picture of risk."

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Even if produce doesn't protect against cancer, it does appear to promote cardiovascular health. Consumption of at least five daily servings of fruits and vegetables is associated with a 30-percent lower risk of coronary heart disease and stroke. Research also hints at a relationship between fruits and vegetables and a reduced risk of diabetes. And produce can displace less-healthy fare in your diet. When you fill your plate with a rainbow of fruits and vegetables, for example, there's less room for red meat—consumption of which has been linked to cardiovascular disease.

Details, Details

It may turn out that the real benefits of such foods as fruits, vegetables, and whole grains are found in the individual compounds they contain.

"We should be looking not just at macronutrients like fat, carbohydrates, and protein, but at micronutrients as well," says C. Ronald Kahn, the Mary K. Iacocca Professor of Medicine at HMS and head of the Integrative Physiology and Metabolism section at Joslin Diabetes Center. To that end, he investigated the effects of leucine, an amino acid found in dietary protein that appears to play a role in insulin signaling. For the study, published in 2011 in *PloSOne*, he and his team gave rats twice the normal amount of leucine in their chow, then fed them either a regular or a high-fat

PHOTO: JIM HARRISON/HARVARD STAFF PHOTOGRAPHER

diet. They found that the rats receiving extra leucine showed reductions in blood sugar levels and less fat in their livers. High blood sugar and fat harbored in the liver can contribute to what is known as metabolic syndrome, an array of medical disorders that, taken together, can increase a person's risk for cardiovascular disease and diabetes. The rats were also better able to respond to insulin production and to handle glucose, even though leucine didn't help them lose weight. "Adding just this one amino acid to the diet changed the metabolism in a lot of different pathways," says Kahn. "It's evidence that even a small dietary change can make a big difference."

Folate, a B vitamin found in such foods as leafy greens, legumes, sunflower seeds, and orange juice, also shows promise for good health—but only in some people. Once touted for its potential to reduce the risk of heart disease, folate has had disappointing effects in many studies. "This is another case where we need to look at the specific populations being studied," says Ding. He points out that studies of U.S. men and women show little cardiovascular benefit from this vitamin, but adds that very few Americans are deficient in folate. "But meta-analyses," Ding notes, "actually suggest that folate may indeed help prevent stroke in people who have low blood levels of it."

A similar careful approach to nutrition research may someday shed light on the health effects of vitamin D, says Ding. Found in seafood, dairy products, and fortified cereals, this vitamin is being heavily studied for its role in diseases as diverse as osteoporosis, multiple sclerosis, diabetes, and prostate, breast, and colorectal cancers. Yet researchers still need to tease out many of the particulars, including refining what blood levels of the vitamin are optimal and whether the vitamin prevents the onset or worsening of these diseases.

Food Fight

For many nutrition researchers, the work doesn't end in the lab. Instead, they are using their findings to help educate consumers; overhaul the food available in schools, hospitals, and workplaces; and in some cases, even change public policy. Willett and colleagues have created research-based versions of the USDA's food pyramid and healthy plate icons, aimed at helping people make healthier meal choices without the influence of lobbyists, an influence that sparked criticism of the government's guidelines. He hopes that hospitals and schools will begin applying these dietary recommendations to their cafeterias. Although Willett was instrumental in improving the culinary choices offered at the Harvard School of Public Health, he finds that the fare at some Boston-area hospitals remains dismal and that many academic institutions are still failing nutritionally. "These places," he says, "are literally feeding the obesity epidemic."

Ludwig also advocates for dietary changes that encourage both children and adults to achieve and maintain a healthy weight. "Highly processed foods and sugary drinks have become the basis of the American diet," he says. "We need to start implementing intelligent public health actions, including increasing educational programs, overhauling school cafeterias, and placing sensible taxation on junk foods and beverages."

Ding, in fact, is currently involved in a movement in Slovenia to begin taxing sugar-sweetened beverages, and he hopes to see the same happen here someday. Yet he knows that such a victory would be just one small step in the journey to better nutrition. "Access to inexpensive, nutritious food is a huge roadblock in many communities," he says. "The price of fruits and vegetables has outpaced the rate of inflation, and the poor in this country have become poorer. It's a double whammy."

Change comes slowly in the worlds of both nutrition and government, and the major structural shifts needed for public policy progress may still be decades away. Meanwhile, investigators hope that their work will help inform what ends up on consumers' plates—and how it affects their health. "Nutrition," says Ding, "is about much more than just what to eat."

Jessica Cerretani is a Boston-based health and medical writer.

LIFE SUPPORT

AT ITS MOST BASIC, food keeps us alive. And while your main concern about nutrition may be what to make for dinner tonight, nourishment takes center stage for someone who is critically ill or injured. Until about 50 years ago, patients with severe intestinal damage that prevented normal digestion found themselves in a fear-filled race against time: Would their organs heal before they starved to death?

Fortunately, parenteral nutrition has made that fear a thing of the past. In this feeding technique, a catheter delivers a liquid blend of glucose, amino acids, and lipids directly into a patient's bloodstream, completely bypassing the gastrointestinal system. It is "one of the great medical inventions of the past century," says Bruce Bistrian, chief of clinical nutrition at Beth Israel Deaconess Medical Center and an HMS professor of medicine. "It allows us to nourish sick people as long as necessary."

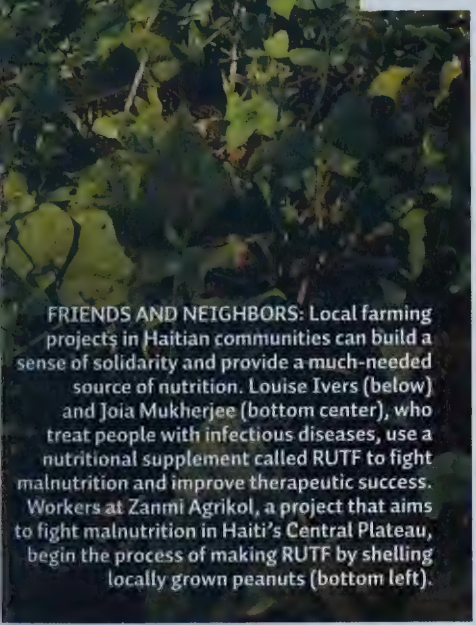
Parenteral nutrition is not without controversy: its use can increase the risk of infection. This drawback has led some physicians to prescribe enteral nutrition, which introduces nutrients directly into the stomach through a tube, for critically ill patients whose intestines still function. Yet a meta-analysis published in *Intensive Care Medicine* in 2005 found that the mode of feeding patients in intensive care units—whether enterally or parenterally—may matter less in terms of mortality and morbidity than in the timing and amount of nourishment. Providing critically ill patients too much glucose, for instance, can be problematic. "We're discovering," says Bistrian, "that starting enteral and parenteral nutrition as soon as necessary and limiting caloric intake to 50 to 70 percent of the daily recommendation decreases the patient's chances of becoming hyperglycemic, which in turn may lower the risk of infections."

Some research suggests that this caloric calibration approach may even reduce the inflammatory response of the underlying illness or injury—a dampening action that could potentially speed healing.

Now a regular tool for physicians, parenteral nutrition continues to be fine-tuned. "It's a well-established therapy," says Bistrian. "But we still have much to learn."

—*Jessica Cerretani*

Can peanuts heal a malnourished nation? BY KARIN KIEWRA



FRIENDS AND NEIGHBORS: Local farming projects in Haitian communities can build a sense of solidarity and provide a much-needed source of nutrition. Louise Ivers (below) and Joia Mukherjee (bottom center), who treat people with infectious diseases, use a nutritional supplement called RUTF to fight malnutrition and improve therapeutic success. Workers at Zanmi Agrikol, a project that aims to fight malnutrition in Haiti's Central Plateau, begin the process of making RUTF by shelling locally grown peanuts (bottom left).

PHOTOS: COURTESY OF PARTNERS IN HEALTH; COURTESY OF MATTHEW LESTER (BOTTOM CENTER); STOCK.XCHNG (ABOVE RIGHT)

Ground Force

Consider the peanut, the simple groundnut, a staple of ballparks and beer gardens in this country, and, when sporting a top hat and a monocle, an internationally recognized trademark for snack products. But now consider that the peanut, this everyman's legume, just might be the fuel for a nutritional revolution—one that could, in a cost-effective and sustainable manner, improve the chances for therapeutic success among millions of people suffering from infectious diseases in developing countries.

Infectious diseases such as HIV and multidrug-resistant tuberculosis can swiftly wipe out the body's immune defenses. In the battle against these and other diseases that disproportionately afflict the poor, medications are indispensable. But so is food, says Joia Mukherjee, an HMS associate professor of global health and social medicine.

"Nutrition underlies everything," says Mukherjee, who, as chief medical officer for the international care organization Partners In Health, has cared for the sick in such low-income countries as Haiti, Lesotho, Malawi, Peru, Russia, and Rwanda. "The link between chronic malnutrition and infectious killers—including malaria, cholera, and pneumonia—is very tight."

And it's not just a matter of calories. The right blend of proteins and fats is essential; without it, the immune system becomes deranged, hastening death long before malnutrition itself can cause irreversible tissue and organ damage. To address this, Mukherjee and colleagues treat severe malnutrition using ready-to-use therapeutic food, or RUTF. This nutritional supplement can take a couple of forms, but a popular one is a high-calorie blend of peanuts, oil, sugar, milk powder, vitamins, and minerals.

Louise Ivers, an HMS assistant professor of global health and social medicine, and senior health and policy advisor for Partners In Health in Haiti, is comparing the health impact of two kinds of RUTF: the peanut mixture and another made of rice, oil, and sugar augmented with corn and soy. In the initial stages of a consumptive disease, the body burns calories at a heightened rate, so getting nutrients to patients early in the course of infection can save lives. Backed by National Institutes of Health funding, and employing focus groups, direct health measures, and proxies for health status—for example, children's school attendance—Ivers aims to highlight how food affects the fragile societal safety nets on which life also depends.

That nutritional supplements such as RUTF work in beating back disease is abundantly clear. "We've shown they're associated with better clinic attendance and greater weight gain," Ivers says, citing her 2010 study in *AIDS Research and Therapy*. Maximizing food's power to cure and prevent disease is an ambitious goal, she concedes—but one that offers a durable lifeline to millions worldwide.

Karin Kiewra is editorial director for the HMS Office of Communications and External Relations.

SURVIVOR: Bristlecone pines can thrive for thousands of years in arid, high-altitude landscapes by following what some might consider a botanical version of calorie restriction.

A pinch of food and a dash of stress may lead to a long life BY JAKE MILLER

Stone Soup

Imagine a plate filled with vegetables, vibrant with color. They're sprinkled with nuts, drizzled with extra-virgin olive oil, and topped with a tidy serving of grilled salmon or, perhaps, tofu. Sliced strawberries decorate the plate's edge. Now imagine scraping away a sizable wedge—as much as a third—of that meal. Even worse, imagine this subtraction occurring day in and day out, whisking away food and nearly half the calories of each meal. ■ Such spare servings aren't simply a formula for weight loss. They're part of a considered lifestyle based on the idea that a lean life might lead to a longer life marked by fewer age-related diseases and slowed senescence. On the edge of starvation, deep in the heart of hunger, some believe they have found the fountain of youth.

SLOW BURN: Some tortoise species live 150 years or more.

In just about every creature in which calorie restriction has been tested—brewer's yeast, bacteria, roundworms, and mice—it has lengthened the life span of the species, sometimes nearly doubling it.

A Slim Edge

The roots of this belief can be traced to evolutionary changes incorporated billions of years ago into the genes of living organisms. When severely stressed, as when an organism is hungry almost to the point of starvation, running repeatedly from unrelenting predators, or chasing ever-elusive prey, cells within the body open chemical pathways that increase the efficiency of energy processing and speed up the repair and recycling of damaged proteins, allowing the organism to survive. In humans, these responses improved our chances for survival throughout the millennia. But scientists think stress responses may have another role: they may help prevent cancer, diabetes, and other diseases associated with aging.

"Since the ancient Greeks, we've known that exercising and eating less or fasting is good for you, but we've never really known why," says David Sinclair, an HMS professor of genetics and a codirector of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard Medical School.

Sinclair studies sirtuins, a family of genes found in most living things. He thinks these genes may play key roles in the stress-related responses that protect us against disease and increase our chances for living longer and remaining healthy. In addition, Sinclair and other scientists think that therapeutics based on sirtuins or their activity may help trigger the genes and biochemical pathways that control the effectiveness of our disease defenses, which may become less active as we age.

Less Is More

Currently, the best understood means of triggering a cascade of anti-aging defenses is calorie restriction. Research has shown it plays a crucial role in preventing obesity, fighting diabetes, preventing tumor growth, and metabolizing fat. There's also evidence that, while calorically restricted animals become infertile while they are hungry, once they start to eat again they can delay menopause and extend fertility much later into life than normal.

The first experiments on calorie restriction, which took place during the Great Depression, were conducted on rats. Researchers cut back the amount of food they gave to the animals and expected to see the animals' health deteriorate. Instead, the rats' health improved, and they lived longer. In just about every creature in which calorie restriction has been tested—brewer's yeast, bacteria, roundworms, and mice—it has lengthened the life span of the species, sometimes nearly doubling it. What's more, vitality remained high even as age increased.

Humans already have a long life span. In fact, only a few species of animals outlive us: Some tortoises live for 150 or so years, and bowhead whales may achieve 200 years. Certain plant species, like the bristlecone pine, live thousands of years in the austere environments of the arid southwestern United States. Interestingly, the bristlecone and similar long-lived plants might be said to practice a botanical version of calorie restriction.

Our long life span makes it difficult to measure the outcomes of calorie restriction. But one attempt, a short-term test, is found

PHOTOS: SCOTT T. SMITH/CORBIS (PREVIOUS SPREAD); STOCK.XCHNG (PREVIOUS PAGE AND LEFT); COURTESY OF JOSLIN DIABETES CENTER (BLACKWELL, OPPOSITE PAGE); KRIS SNIBBE/HARVARD UNIVERSITY NEWS OFFICE (SINCLAIR)

in research undertaken during World War II. A group of conscientious objectors volunteered to adhere to a diet that approximated the levels of deprivation found in the war-devastated regions of Europe. Scientists found that the participants not only experienced ravenous hunger, but that they were also constantly irritable. More troubling were the instances of participants suffering severe psychological troubles, including self-mutilation. One participant attempted suicide.

A contemporary, nonscientific look at the long-term effects of calorie restriction can be found among the thousands of members of the Calorie Restriction Society, based in New York. Society members voluntarily restrict their calorie intake by at least 25 percent of what might be considered normal for a healthy adult. They do this out of a conviction that by radically lowering their caloric intake, they will prolong their lives and stay healthy into their old age. Many adherents have steadfastly practiced their lean eating regimen for more than a decade.

Unfortunately, many people find it almost unimaginably hard to maintain this sort of diet. To achieve it, a moderately active 155-pound male would need to cut his intake from around 2,500 calories a day to around 1,800 calories, the caloric intake recommended for a minimally active male weighing less than 130 pounds. And cutting back to such spartan amounts is not the only challenge; in order to maintain healthy levels of key nutrients, the calories must be well chosen. That leaves precious little room for French fries or even low-fat French vanilla yogurt.

Round Round Get Around

For those who despair that they haven't the will power to follow such a lean diet, yet still would like to enjoy a long, healthy life, there is good news. According to ongoing longitudinal studies of centenarians, most people who live extraordinarily long lives don't follow calorie restriction. They also often don't work out, or do anything else intended to prolong their lives.

Some early theories of aging posited that we grew old as we consumed our lifetime allotments of physiological actions—a quantum of calories to metabolize, a quantity of breaths, or a quota of heartbeats, for example. It was initially thought that calorie restriction worked because it slowed the body's clock and its inevitable ticking toward the end of life. It turns out that it's not the act of eating or processing fewer calories that matters. People who eat what they like, skip exercise, enjoy life, and still remain active for more than 100 years may simply have more robust repair processes than most of their peers.

These carefree super-centenarians give T. Keith Blackwell, an HMS professor of genetics at the Joslin Diabetes Center, hope for the field of aging research. "People who live past about 104 tend to be surprisingly healthy. Until they get a serious infection or the body just stops working, most of these super-centenarians are up and around and energetic," he says.

One goal for researchers who study aging, Blackwell says, would be to find a much simpler way to achieve a vital, disease-free old age than by calorie restriction—perhaps a drug, a particular pattern of exercise, or tweaking certain nutrients in the diet.

To find that simpler way, Blackwell has been researching *skn-1*, a gene-regulating protein found in the much-studied roundworm *Caenorhabditis elegans*. This regulator is analogous to regulatory proteins coded for in the human genome. *Skn-1* plays multiple roles in the life of a roundworm: It helps build its digestive system; it manages the recycling of wastes and toxins that contribute to its aging, and it triggers several of the roundworm's longevity pathways.

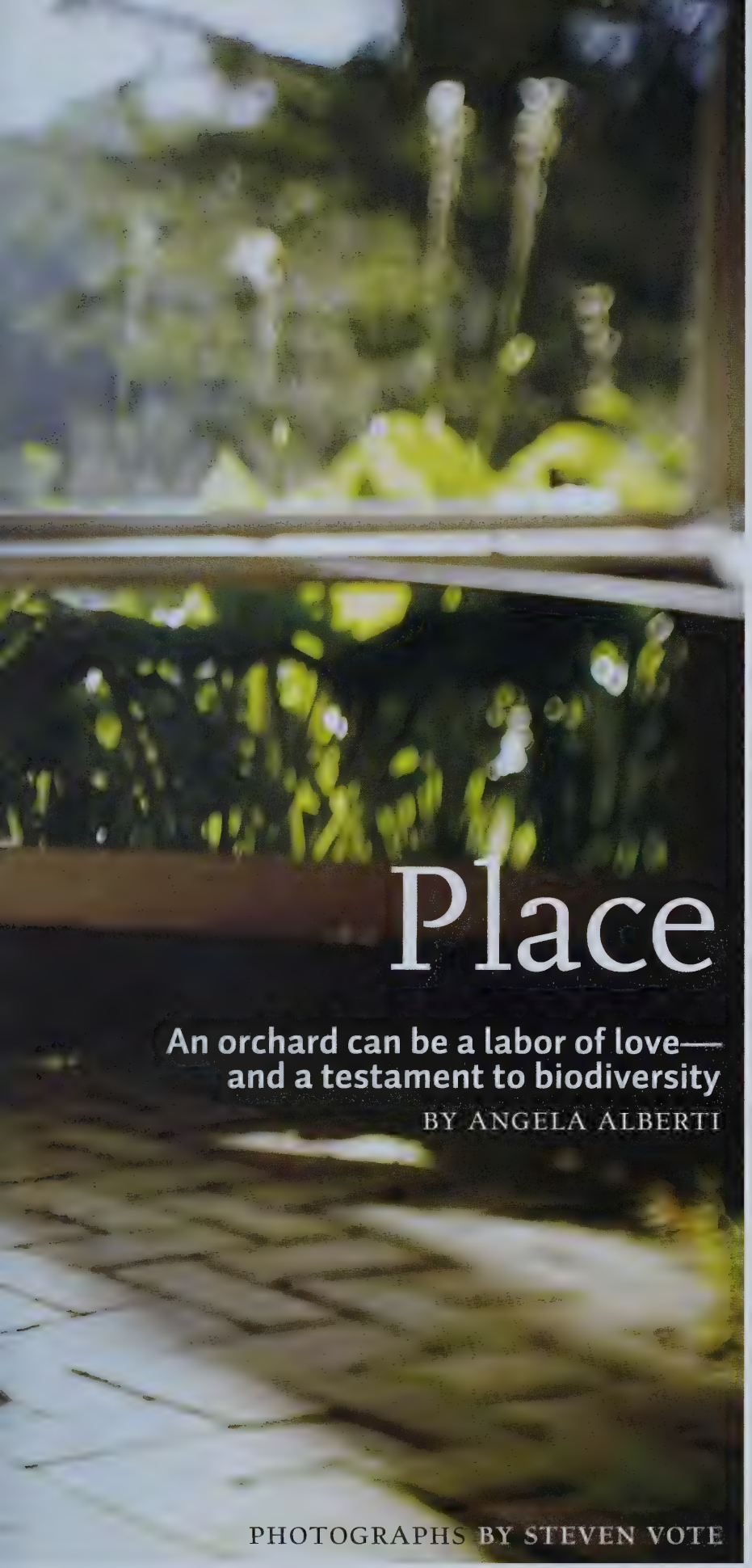
Blackwell has found that *skn-1* is important to *C. elegans* in a variety of stress situations, not only when the organism undergoes calorie restriction. "Stress defenders talk to other stress defenders and help each other out," he says. It seems that there are many different stress-response processes and that they work together, back each other up, trigger, and reinforce one another in rather complicated ways.

But how do we get these processes talking to one another when we need them most? How do we make it so that we all can benefit from these life-prolonging powers?

"The complexity of this process at the nano scale is mind-blowing," Sinclair says. "And the challenge is to try to find a medicine that can directly tweak that system without causing any side effects at the nano level. It is going to take the careers of many people to get there."

STRESS TESTERS: Researchers such as T. Keith Blackwell (left) and David Sinclair investigate how calorie restriction and other physiological pressures might prevent diseases that are associated with aging.

Jake Miller is a writer and editor in the HMS Office of Communications and External Relations.



Place Setting

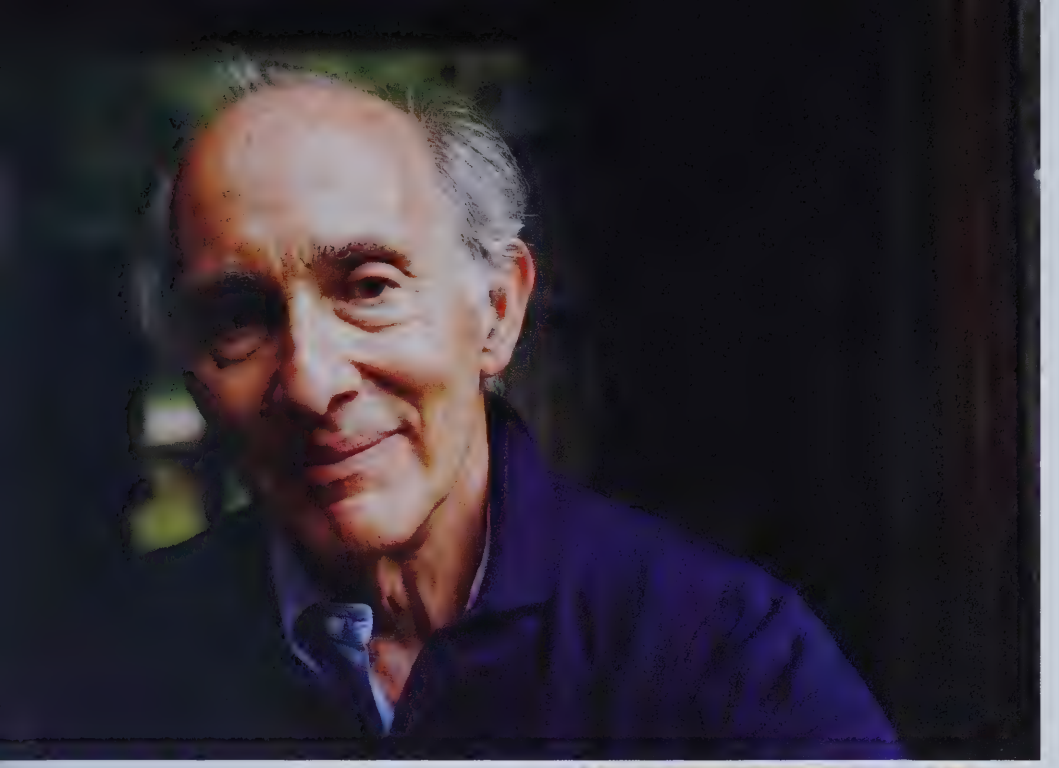
An orchard can be a labor of love—and a testament to biodiversity

BY ANGELA ALBERTI

PHOTOGRAPHS BY STEVEN VOTE

A glint of turquoise passes in front of him as he stands quietly, one hand wrapping a yellow coffee mug. The dragonfly lightly touches Eric Chivian's shoulder. Once. Twice. Then, it zooms away, its color blurring, its whisperless flight threading through the buzzes, chirps, and song that fill the morning air. The hum of daily life on his 42-acre farm and orchard in central Massachusetts pleases Chivian '68. So does the knowledge that history is rooted all around him. And he savors the names that go with that history: Newtown Pippen. Esopus Spitzenberg. Ashmead's Kernel. Roxbury Russet. ■ These are just a few of the seventeenth- and eighteenth-century heirloom apples that Chivian, an HMS assistant clinical professor of psychiatry, has nurtured in his orchard for

THE DEPTHS OF BEAUTY: Just as the understated grace of stove and chair in Eric Chivian's home quietly attests to purpose and function (far right), the natural splendor of heirloom apples speaks to a genetic lineage that preserves flavor and stamina.



nearly two decades. And although he is connected to the past through his orchard, it's Chivian's hope that the sustainable methods he uses to cultivate his trees—together with his dedication to fostering biodiversity in agriculture—will help protect the health of Earth and its people for years and generations to come.

Johnny Appleseed

When not enjoying the ambience of his acreage, Chivian works to interest and enlist his fellow physicians in efforts to protect the environment and to increase public understanding of the potential health consequences of global environmental change. His dedication to these goals led him, in 1996, to found the Center for Health and the Global Environment at Harvard Medical School. But this was not Chivian's first effort to spur physicians to social action. In 1980, he cofounded the International Physicians for the Prevention of Nuclear War. The efforts of this group brought its founders, all members of Harvard's faculty, the 1985 Nobel Peace Prize.

"Physicians can greatly influence public opinion and policy that relates to health issues. Alterations to the environment ultimately affect human health on every level," he says. "Food is definitely a health issue. I'm interested in how changes to the environment affect food, the food supply, and biological diversity."

Biological diversity, or biodiversity, is simply the variety of life in an ecosystem. In an agricultural ecosystem, this includes the microbes that live in the soil and make it fertile, the above-ground insects that pollinate and protect crops against pests, and the range of plant species that grow within a self-sustaining area.

Agribusinesses, as the larger industry-affiliated farms came to be known, drastically reduced the variety of food grown. Today, just 12 plant species provide nearly 75 percent of the world's food supply.

Seed Catalog

Chivian's interest in food and food production started when he was young. His family planted a backyard garden during World War II, part of a national effort to help alleviate food shortages. But it was family trips to a local cider mill that sparked his lifelong interest in apples. "The cider would just pour out of the press," he says. "And the smell! It was magic to me."

Since the days of those backyard Victory Gardens, agriculture in the United States has undergone a revolution. According to the U.S. Department of Agriculture, in 1940, there were more than six million farms in this country; by 1997, that number had decreased 70 percent, dropping to just shy of two million. By contrast, during that same period, the average farm size increased nearly threefold, from an average of 174 acres to 487.

Agribusinesses, as the larger industry-affiliated farms came to be known, drastically reduced the variety of food grown, by focusing on a handful of crops, such as corn, wheat, and soy. Today, just 12 plant species, primarily starch-rich commodities such as grains and beans, provide nearly 75 percent of the world's food supply. "The vast plant monocultures that large-scale farming produces not only strips us of the diversity of plant life, but it also jeopardizes the world's food supply," says Chivian. "Monoculture agriculture is extremely vulnerable to such environmental variations as climate change."

Loss of plant species—and the seeds that they grow from—is not without consequence. Between 1900 and 2000, 75 percent of crop diversity was lost owing to disuse or the disappearance of particular plant varieties, according to a recent report from the U.N.'s Food and Agriculture Organization. In the United States, as elsewhere, this drop in diversity has meant the disappearance of species: More than 80 percent of corn, cabbage, apple, and pea varieties known at the start of the twentieth century are now extinct.

According to Chivian, most varieties of fruits and vegetables available today aren't necessarily the healthiest or even the best tasting. "When food began to be shipped long distances, rather than being grown and sold locally," he says, "there was a movement toward producing food that shipped well and looked beautiful. Unfortunately, sturdiness and beauty often came at the expense of flavor."

Heirloom fruits are often compared to wine because of their complex flavor profiles. And like wine, such fruits are beginning to be appreciated and savored.

GARDEN OF EARTHLY DELIGHTS: Apple varieties that date to the seventeenth and eighteenth centuries share ground in a biodiverse community of birds, insects, and plants such as garlic (right) and coleus (far right).

Soul Food

Like Chivian, Katherine McManus believes the produce in today's grocery aisles is of lesser character than its heirloom counterparts. And, as director of the Department of Nutrition at Brigham and Women's Hospital, she spreads this gospel to her patients. "I do recommend heirloom because I think they taste better," says McManus. "Taste trumps nutrition every time, so when taste and nutrition go hand in hand, so much the better."

In recent years there have been some studies that suggest a general decline in nutrient levels in fruits and vegetables, but there is no consensus on the issue among experts. According to McManus, comparing nutritional values across varieties, also known as cultivars, is difficult because several factors can influence the micronutrient value of a particular food: the soil composition, temperature during growth, fertilization methods, ripeness at the time of harvest, and how far the food was shipped before being eaten.

A 2001 review of more than 400 research reports by the United Kingdom–based Soil Association found that vitamin C and mineral content may be higher in organically grown crops. More recent studies report higher

levels of disease-fighting phytochemicals in organic varieties compared with their conventionally grown relatives. In addition to a possible improvement in nutritional profile, organically grown foods do not depend on the use of chemical insecticides and petroleum-based fertilizers. In the years 2000 and 2001, according to the U.S. Environmental Protection Agency, more than five billion pounds of pesticides were applied to crops grown conventionally throughout the world.

"We lack a real food culture," says McManus. "Buying whole foods, supporting our farmers, and doing more of our own cooking are key to improving that culture. If we had a better appreciation for food, we might be better able to address some of our nation's nutritional issues, such as overconsumption."

According to the Centers for Disease Control and Prevention, obesity rates have spiked throughout the past two decades, with nearly 34 percent of U.S. adults and 17 percent of children and adolescents categorized as obese. McManus thinks a dysfunctional relationship with food may be one cause, a link that may result in type 2 diabetes, cardiovascular disease, and certain cancers.

Palate Pleasers

McManus follows her own advice, and she and her husband organically cultivate a garden of heirloom tomatoes, preferring the

Brandywine and Brandywine Pink varieties. Heirloom fruits are often compared to wine because of their complex flavor profiles. And like wine, such fruits are beginning to be appreciated and savored.

"There's a resurgence of interest in heirloom apples," says Chivian. "Farmers' markets are beginning to carry Roxbury Russets and Baldwins and other incredible apples that had fallen out of favor. And that's all to the good because the flavor of these fruits is magnificent."

Popular culture reflects this renewed interest in the locavore and snout-to-tail food movements, specialty cooking magazines, websites, and food-centric cable television networks like the Cooking Channel and the Food Network.

"It's a really interesting sort of movement in our culture," says Kathleen Frith, managing director of the Center for Health and the Global Environment, "one we wanted to involve Harvard students in."

In April 2010, the students got that chance with the advent of the Harvard Community Garden in Harvard Square. A large plot that includes about 1,200 square feet of raised beds, the organic garden produces 50 varieties of vegetables, including heirlooms with such evocative names as Purple Haze carrots, lemon cucumbers, and fairy tale eggplants.

The Association for the Advancement of Sustainability in Higher Education reports a surge in the number of such campus gardens sprouting on more than 100 U.S. colleges during the past two years. From its most recent poll, the Vermont-based National Gardening Association says that 37 percent, or an estimated 43 million, U.S. households planned gardens in 2009, an increase of 7 million households over 2008 estimates. And the number of farmers' markets is also burgeoning, up 17 percent in 2011 from the previous year and 36 percent from 2009, according to the USDA.

Bringing food production out of the dark and into the limelight is beneficial on many levels: It can lessen the use of fossil fuels to transport food long distances, cutting contributions to climate change; it also helps local farmers build community, which, in turn, can benefit local economies. And then there are the benefits of the food itself, for locally sourced food can be picked at the height of its nutrient content and flavor.

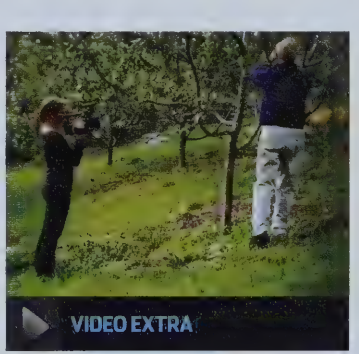
Gentlemen Farmers

Back in his orchard, Chivian picks an apple from an Esopus Spitzenburg tree, a variety that was Thomas Jefferson's favorite. "I'm a biologist and naturalist," he says, "so for me, being a farmer is field biology at its best." He polishes the apple on his shirt and takes a bite.

"The only way to get an Esopus Spitzenburg tree is to cut a branch and graft it onto a root; the genetics is in the branch, not in the seed," he explains. "I love that connection. I love the fact that I have the same tree as Jefferson's, and thus a connection to him."

"This orchard is magical to me," he adds. "There's a power that comes from being connected to the earth. When Jefferson was in his late 70s he said, 'I may be an old man, but I'm still a young farmer.' I agree with him completely."

Angela Alberti is an editorial specialist in the HMS Office of Communications and External Relations.



An Orchard and A Passion:
A Visit with Eric Chivian '68
harvardmedicine.hms.harvard.edu

Market Day: A Guided Tour with Michelle Hauser '11
harvardmedicine.hms.harvard.edu

Medical Toque

When white coats do double duty prescriptions can be tasty

BY JESSICA CERRETANI

Michelle Hauser

Mise en place: Resident physician, Cambridge Health Alliance; Chef, Le Cordon Bleu Diplome; 2009–10 Zuckerman Fellow in public policy, Harvard Kennedy School; achefinmedschool.blogspot.com

PREPARATION: When financial and family circumstances threatened her dream of a career in medicine, Michelle Hauser '11 pursued her second love: cooking. Armed with a degree from Le Cordon Bleu culinary arts program at Minnesota-based Brown College—and an internship at the California foodie mecca Chez Panisse—Hauser taught cooking classes to help pay the bills and, eventually, her tuition for medical school. Despite these dual careers, connecting food and health wasn't automatic for this physician-chef. "I knew that the majority of our disease burden can be prevented by factors like diet," she admits. "But I had always been warned not to teach 'healthy' cooking classes because no one would take them."

PLATING: That changed when Hauser's students discovered that she was a vegetarian and challenged her to offer a course in cooking tasty, healthy fare. To her surprise, it was a hit. "The truth is, people are excited about healthy food," she says. "But they won't sacrifice taste." These days, Hauser combines her culinary knowledge with her medical training through workshops that educate patients with chronic conditions like hypertension or diabetes about healthy food choices. She's also interested in increasing community outreach and helping develop public policy approaches promoting better nutrition. Her biggest success, however, may be as a role model: Even as a busy resident, Hauser manages to eat a diet that's rich in vegetables, fruit, and whole grains. "If I can do it, anyone can," she says. "You just need to figure out what works best for you."

Andrew Weil

Mise en place: Founder and program director, Arizona Center for Integrative Medicine; Cofounder, True Food Kitchen www.truefoodkitchen.com; Bestselling author of ten books, including *Eating Well for Optimum Health* and *The Healthy Kitchen*

PREPARATION: He's no stranger to soy milk. He was eating black cod with miso long before hot eateries like New York City's Nobu made it cool. He grows his own kale; organic, should you wonder. Yet Andrew Weil '68 wasn't always so selective about the food that sustains him. Banned from the kitchen as a child, he had little culinary experience until a world-spanning trip at age 17 opened his eyes to ethnic cuisines. Later, during his medical residency, Weil began cooking for himself as a way to temper the long hours spent on the wards. "Hospital food was dreadful," he says. "I found that envisioning a meal that would give me pleasure and satisfaction, then creating it, kept me healthy, physically and psychically."

PLATING: Weil has long shared his passion for nutrition with both patients and the general public. A firm believer that food is often the best medicine, he recommends following an anti-inflammatory diet that's high in fruits, vegetables, whole grains, and fish, and low in processed foods. Although smart food choices can be easy at home, Weil admits such choices can be slim when dining out. But Weil aims to change that through a collaboration with restaurateur Sam Fox. In 2007, when the two met, "Sam thought healthy food meant tofu and sprouts," Weil laughs. "I set out to prove him wrong." It wasn't easy: Even after cooking dinner for Fox and his wife, it took a meeting with chef Michael Stebner to prove that fresh, local food could also be delicious. Today, Weil and Fox head a national chain of True Food Kitchen restaurants, where Stebner's menu offerings include grilled salmon, spaghetti squash casserole, and orange-olivello sorbet. And Weil is discovering that the way to the public's heart may, indeed, be through its stomach. "Showing people that healthy food can be delicious," he says, "may be more powerful than any amount of writing I could do on the subject."

A firm believer that food is often the best medicine, Weil recommends following an anti-inflammatory diet that's high in fruits, vegetables, whole grains, and fish, and low in processed foods.

PHOTOS: JOHN SOARES (PREVIOUS SPREAD); COURTESY OF WEIL LIFESTYLE

Daphne Miller

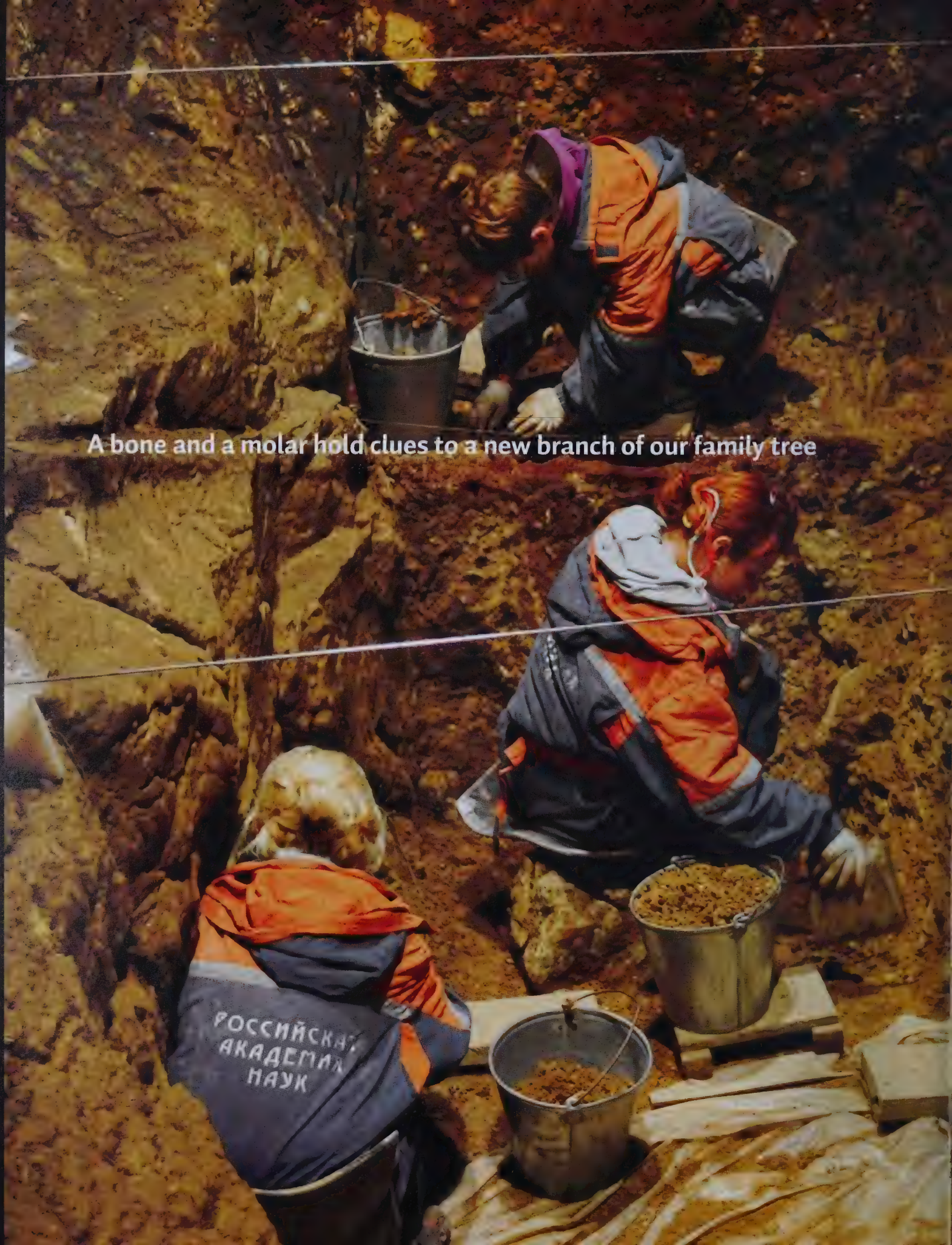
Mise en place: Integrative family medicine physician, San Francisco; Author, *The Jungle Effect: A Doctor Discovers the Healthiest Diets from Around the World—Why They Work and How to Bring Them Home*; Associate clinical professor, Department of Family and Community Medicine, University of California, San Francisco; drdaphne.com/wordpress

PREPARATION: For Daphne Miller '93, the seeds for eating well were planted early: With both parents in the Peace Corps, she grew up in areas where people valued food as much for its cultural and medicinal powers as for its gastronomic aspects. This point was underscored when she began a residency at San Francisco General Hospital, working with a low-income, multicultural population. "Patients would ask me questions like, 'Why did my Mexican grandmother live to age 95, but I'm sick with diabetes?'" she says. "Chances are the grandmother ate a diet that was completely different from that of the grandchild. And she probably connected to food in a whole different way, too."

PLATING: That realization soon set Miller on a path to discover as much as she could about traditional diets and culinary customs. She spent three years visiting areas where the local populations have low chronic disease rates—Cameroon; Copper Canyon, Mexico; and Iceland—and learning their dietary customs and recipes. Her investigation grew into her 2008 book, *The Jungle Effect: A Doctor Discovers the Healthiest Diets from Around the World—Why They Work and How to Bring Them Home* (Harper Collins). A second book, on the link between farming practices and health, is in the works. Meanwhile, Miller's applying the nutritional lessons learned from other cultures to her patients in San Francisco. "Traditional diets have survived for so long because they taste delicious and keep people healthy," she says. "It's amazing how much I use this information even during routine primary care encounters."

Jessica Cerretani is a Boston-based health and medical writer.

PHOTO: AMANDA MARSALIS PHOTOGRAPHY, INC.



A bone and a molar hold clues to a new branch of our family tree

DOWN TO EARTH: Excavation of Denisova Cave, a site overseen by the Russian Academy of Sciences, is an ongoing venture involving international teams of researchers.

Spelunking for Genes

Perched in the Altai Mountains of southern Siberia, and overlooking the Anui River and its surrounding forest, is the Denisova Cave. It is not a particularly large natural structure, but its high ceilings, central limestone chimney, and location near abundant food sources have made it an inviting shelter for humans and animals for tens of thousands of years.

BY DEBRA BRADLEY RUDER

"It's kind of a magical cave," says David Reich, an HMS professor of genetics who traveled to the site this past summer. It was a rugged trip, covering 5,500 miles on a 48-hour journey that began in Boston, touched London and Moscow, and finished with a bumpy 10-hour van ride to the Denisova Cave, near Russia's border with Kazakhstan. But Reich, whose affiliation with the Broad Institute of MIT and Harvard means he's more often surrounded by gene sequencers than Stone Age tools, took the opportunity to step inside this remote refuge to witness the resting spot of ancient DNA that had been preserved in bone fragments buried deep in cave sediments.

For the past year, Reich and an international team of evolutionary geneticists have been coaxing information from that DNA. What they've found has changed our understanding of human history.

Welcome to the Family

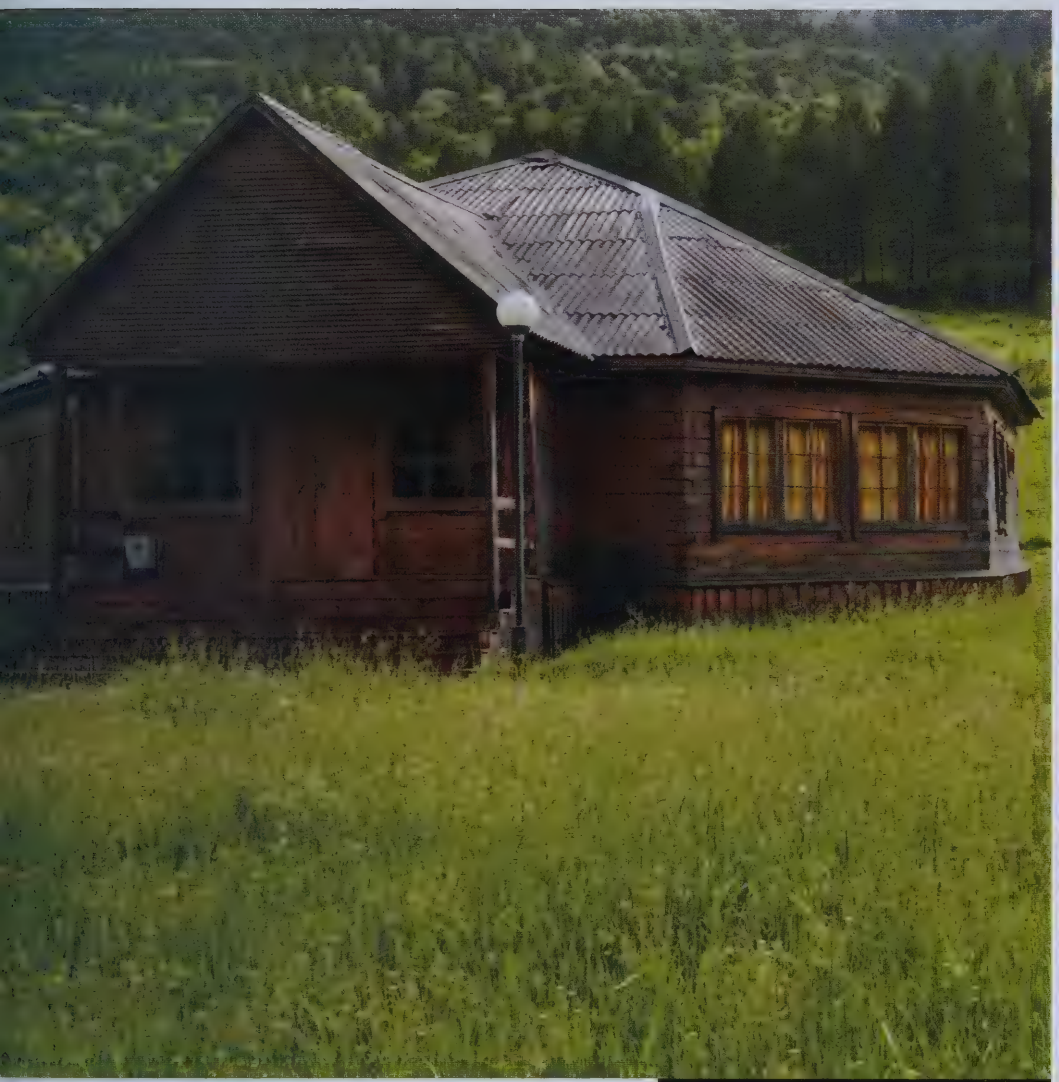
Russian archaeologists have been excavating Denisova Cave for three decades, but it wasn't until recently that they unearthed a pea-sized pinky bone from a young girl who, they think, lived some 30,000 to 50,000 years ago. Remarkably, it contained enough genetic material to salvage and study.

That bone, along with an oversized adult molar, helped Reich and his colleagues at HMS and the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, identify a previously unknown hominin who was neither Neanderthal nor modern human. This "archaic" group, dubbed the Denisovans, after the cave, apparently inhabited a large swath of Asia and—like Neanderthals—mated with modern humans. Although both Neanderthals and Denisovans eventually died out, traces of their genes live on in some populations today.

These discoveries are adding pieces to the puzzle of how humans evolved and where and when prehistoric people roamed the Earth. The work also reinforces the notion that population mixing has been the rule, not the exception, throughout human history. For geneticists like Reich, however, the greatest promise of this research might be in learning whether the genes inherited from these ancient people help protect today's humans from disease.

With the aid of super-fast sequencing and genotyping equipment, the field of modern genetics is expanding knowledge about the past at whirlwind speed, and Reich is at the forefront of that transformation. He and his HMS bioinformatics team have developed complex statistical algorithms for analyzing gene-flow patterns—in this case, for comparing the genomes of ancient and present-day people. "This is an incredibly exciting time to be doing

PHOTOS: COURTESY OF DAVID REICH (THIS SPREAD AND PREVIOUS SPREAD)



A ROOM WITH A VIEW: Denisova Cave is located in the Altai Valley (far left) of southern Siberia. David Reich (above right) worked at the site this past summer, living in accommodations that are part of a permanent camp for teams of researchers.

this work," says Reich. "There's a lot more data than people can make sense of—and the data keep getting better."

Going to the Source

Journeying to Siberia gave Reich a chance to put in context his research on the DNA from that young girl of long ago. He was among a group of 20 geneticists, archaeologists, and paleoanthropologists from the United States, Asia, Europe, and Russia who gathered for the express purpose of learning more about this newfound branch of the human family tree. Although researchers have measured the Denisovans' genetic footprint, they don't have any full skeletons to reference. "Neanderthals are extremely well characterized in the fossil record," says Reich, "but these guys are not. It's DNA in search of a fossil record."

Denisova is so important archaeologically that the Russian Academy of Sciences operates a permanent camp with meeting spaces, a dining hall, and huts with plumbing. A summer visit is definitely the wiser move, though: Winters are frigid, but summers are verdant and temperate.

The group shared findings, visited a dozen archaeological digs, and enjoyed hearty dinners punctuated by vodka toasts. But the highlight for Reich was spending time in the Denisova Cave. According to Russian sources, the hideaway is named after a hermit, Denis, who called it home during the eighteenth century. From their study of the bones and artifacts excavated from the cave, scientists think that Denisovans, Neanderthals, and modern humans all took refuge there at some point. "We don't know any other place where all three groups lived," Reich notes. "That fact gives me a strong sense of continuity with the past."

Where the Bones Are Buried

Archaeologists have dug through 22 layers that step through time from 280,000 years ago to the present. Large objects are bagged, and samples placed in buckets and slid down a wire to a sifting station across the Anui River. That attention to

detail led to the unearthing in 2008 of the pinky bone. It was found in layer 11, a meter-thick stratum laid down over at least the period from 30,000 to 50,000 years ago. In addition to the finger bone and the molar, layer 11 has yielded a Neanderthal toe fragment and a trove of tools and jewelry associated with modern humans.

Reich's involvement in the Denisova project is a bit of scientific serendipity. Svante Pääbo of Leipzig's Max Planck Institute was heading up an effort to decode the Neanderthal genome from bones found in Croatia, and had invited Reich; Nick Patterson, an HMS genetics research fellow; and others to join. The team's findings had just appeared in *Science* in May 2010 when surprising news came from Germany.

"The Leipzig group constantly screens material from various archeological sites," Reich says. "They were screening bones from the Altai Mountains site and noticed the teeny finger bone. I'm shocked that people even knew it was a human finger bone."

The shocks did not end there. After painstakingly drilling into the bone and grinding up the extract, the investigators learned it contained an impressive amount of genetic material, both mitochondrial and nuclear DNA. Reich's team studied the ancient genome's nucleotides, along with DNA sequences from a molar recovered from the cave, and realized the sequences were related to some sequences in Neanderthal DNA.

"We know it's not a Neanderthal because all Neanderthals are quite closely related genetically. This was a very distant relation. It's actually a sister group to the Neanderthals." Their analyses also revealed that Denisovans bred with the ancestors of present-day New Guineans and other Melanesians. This discovery led to the team's second much-heralded paper of 2010, that one in *Nature* in December.

ANCIENT HISTORY: The layers of sediment excavated in Denisova Cave (below) and its surroundings have yielded such artifacts as chipping tools (below right), a fragment of a pinky bone, and a molar. DNA in the bone and molar led to the identification of a new hominin group, the Denisovans.

Delving deeper into the data, the team found that Denisovans lived across a vast area that ran from southern Siberia to Southeast Asia, and that they contributed genes to several populations in Southeast Asia and Oceania, including Australian aboriginal peoples. Interestingly, however, the researchers did not find genetic traces of Denisovans in other groups in this region, including mainland Asians. These findings, the scientists note, suggest that modern humans settled Asia in more than one wave of migration.

Scholars have long debated what happened when modern *Homo sapiens* emerged from Africa 50,000 or more years ago. The work of Reich, Pääbo, and their colleagues offers some insight by indicating that those early humans mixed with both Neanderthals, who inhabited Europe and the Middle East, and the Denisovans in Asia. In fact, the scientists found that today's non-Africans inherit 2.5 to 7.5 percent of their DNA from Neanderthals and Denisovans.

Vintage Accessories

The medical benefits of this research have yet to be fully fathomed. Our Stone Age forerunners passed on traits that modern humans may have used to adapt to new environments, says Reich.

"It will be exciting to see if and how these variations had consequences for disease risk as well," he adds. A study by Stanford University scientists who examined the genomes suggests that Neanderthals and Denisovans helped boost the immune systems of future generations by contributing alleles associated with the human leukocyte antigen system, which helps the body recognize disease-causing germs.

Practical matters aside, Reich finds these pursuits intellectually and personally satisfying. "I feel that part of being human is to be curious; to learn about who we are, where we came from, and the nature of the world we live in," he reflects.

Near his desk in his Boston office, Reich keeps a clear plastic box. In it are two small cream-colored casts, one of the Denisovan pinky bone and the other of a molar found in the cave. They are tangible reminders of the ancient people who inspire his very modern work.

Debra Bradley Ruder is a Massachusetts-based education and health care writer.

PHOTOS: COURTESY OF DAVID REICH (OPPOSITE PAGE); COURTESY OF THE MAX PLANCK INSTITUTE FOR EVOLUTIONARY ANTHROPOLOGY (ABOVE AND RIGHT)

AIDS AT 3

A shape-shifting virus continues to perplex researchers BY SCOTT P. EDWARDS

It was a bold promise made on an April day in 1984. Secretary of Health and Human Services Margaret Heckler proclaimed that a preventive vaccine for a newly identified virus named human T-lymphotrophic virus type III, or HTLV-III, would be available within two years. Many scientists who heard her claim shuddered. ■ More than 27 years later, the chill those researchers felt is understandable. For while the promise and confidence of Heckler's statement have dulled, the virus, now known as human immunodeficiency virus, or HIV, has carved a deep niche, becoming a global threat that, according to UNAIDS,

infected 2.7 million people throughout the world in 2010. In addition, that same year saw an estimated 34 million people worldwide, more than 1 million in the United States alone, living with HIV or AIDS, the syndrome of illnesses the virus can spawn. And in 2010, 1.8 million people died of AIDS.

In the shadow of these numbing statistics, researchers worldwide toil to develop a vaccine to stymie the virus. This global network of investigators includes many at Harvard Medical School. The perseverance of these scientists is fierce, as is their conviction that a vaccine will be found.

Target Practice

"Finding a successful vaccine is challenging," says Ruth Ruprecht, an HMS professor of medicine, cancer immunology, and AIDS at Dana–Farber Cancer Institute, "because we're shooting at a moving target."

The virus has an uncanny ability to mutate as it replicates, producing different strains, each with its own molecular idiosyncrasies and clinical manifestations. Further, HIV has distinct subtypes, or clades, each of which is associated with a specific geographic region. Another difficulty for researchers, then, lies in developing a vaccine that will offer protection against all HIV clades.

The virus' ability to mutate also makes the use of traditional vaccine strategies—a killed form of the virus or an attenuated form, which is live but weakened—risky and impractical. In general, vaccines try to mimic the body's response to an infection, but the traditional paradigms of vaccine development don't hold with HIV. Although in many cases the body eventually develops antibodies against HIV, these antibodies develop too late in most people infected with the virus, giving it too many chances to mutate and thus escape the actions of neutralizing antibodies.

"Historically, vaccines have quite clearly been our most potent weapon against viral diseases of medical importance," says Ronald Desrosiers, an HMS professor of microbiology and immunology. "The list of diseases controlled or eliminated from the face of the Earth by vaccines is impressive."

HMS scientists have spent the past two decades searching for the right combination to unlock the HIV vaccine mystery. Although none of their attempts has resulted in the perfect vaccine, their investigations have provided key information on the biology of AIDS and have laid the foundation for future efforts.

UNFLAGGING EXPLORERS: Researchers Bruce Walker and Ruth Ruprecht are two among many at HMS who persevere in the effort to identify molecular idiosyncrasies of HIV that may serve as targets for a vaccine.

2.7 million infections in 2010

1.8 million deaths in 2010

Control Panel

Bruce Walker, an HMS professor of medicine and the director of the Ragon Institute at Massachusetts General Hospital, MIT, and Harvard, is one of the researchers who has dedicated much of his career to the study of HIV. He leads an international research effort to understand how HIV infection in some people is controlled spontaneously, without medications.

More than five years ago, Walker and his colleagues began studying the genetic characteristics of nearly 1,000 people around the world who are so-called HIV controllers. Though infected with HIV, these people keep their viral load, a measure of the severity of an infection, below 2,000 virus particles per milliliter of blood; a subset called elite controllers keep it below 50. The average untreated HIV patient has, by comparison, a peak viral load of more than 5 million particles per milliliter at the time of acute infection.

"HIV is all about viral load," Walker says. "If a vaccine could keep the viral load below 2,000 particles, we might be able to stop the progression of the disease and transmission might be contained. If you could then replicate this in everybody, the disease would go away."

Other HMS researchers have looked at the effectiveness of vaccine types. The safety of a live, attenuated HIV vaccine, for example, has been debated by researchers for years. In 1992, as other HIV vaccines were failing, a research team led by Desrosiers re-evaluated the risks of a live vaccine by inoculating an animal model with a genetically altered live version of SIV, the simian form of HIV. Three years after vaccination, the animals' immune systems had mounted a successful defense against SIV: They were protected against the disease. At the time, Desrosiers' work was a defining moment for live vaccines; however, subsequent trials of this type of vaccine failed.

In an animal-model study published in *Nature* in January 2012, Dan H. Barouch, an HMS professor of medicine, and a team of scientists at Beth Israel Deaconess Medical Center showed that an experimental HIV vaccine could partially protect animals against an aggressive, virulent form of SIV. Two different vaccine approaches reduced the chances of infection per virus exposure by 80 to 83 percent. In addition, viral loads were significantly reduced. Although the protection was only partial, the study could become a tipping point for HIV vaccine development for humans: It is among the first to show infection prevention against a difficult-to-block, HIV-like virus.

PHOTOS: JUSTIN IDE/HARVARD NEWS SERVICE (OPPOSITE PAGE); COURTESY OF RUTH RUPRECHT

In 2008, Barouch, together with Lindsey Baden, an HMS assistant professor of medicine and an infectious disease specialist at Brigham and Women's Hospital, spearheaded one of the School's first human tests of an HIV vaccine. Vaccines use a vector, or chemically weakened virus, to stimulate an immune response. Many HIV vaccine candidates have used an adenovirus serotype known as Ad5, which commonly causes respiratory infections such as the common cold, as a vector. Ad5, however, is so common in the environment that many people harbor a pre-existing immunity to it, making it ineffective at inducing an immune response to HIV. For this ongoing trial, Baden and Barouch gave 60 healthy volunteers two or three immunizations using another vector, Ad26, or adenovirus serotype 26. This adenovirus is less commonly encountered in the general population, but it has the ability to induce a potent immune response. Testing of this vaccine candidate is currently underway in sub-Saharan Africa.

The HIV vaccine field reached a turning point in 2009 when researchers reported that a prime-boost approach, one designed to kill cells infected with HIV and to prevent HIV from gaining a foothold in an uninfected person, had cut the HIV infection rates among participants in a large clinical study conducted in Thailand. The prime-boost approach combined two vaccines, which had separately failed to be effective. When mixed together, however, the duo cut the infection rate by 31 percent—not enough of a decrease to make the vaccine combination feasible for widespread human use, but certainly enough to suggest that the development of an HIV vaccine may indeed be possible. Interestingly, Barouch's recent study sheds light on this result, indicating that antibody responses to the envelope protein on the surface of the virus may have contributed to the effectiveness of the vaccine.

Pushing the Envelope

A study by Ruprecht recently identified a portion of HIV's envelope protein as a promising vaccine target. A contorted strand of the protein, known as the V3 loop, was originally thought to be an unlikely target because it is highly changeable. However, a portion of the V3 loop known as the crown is conserved and, thus, provides an attractive bull's eye; antibodies aimed at it may protect against multiple strains of HIV.

Ruprecht introduced a monoclonal antibody, a laboratory-produced substance that binds to specific molecules, into an animal model. The monoclonal antibody was isolated from a person infected with a specific HIV clade. The researchers then tested a hybrid virus made from SIV and the envelope from a different HIV clade in the animals. While the researchers knew the monoclonal antibody would attach itself to a portion of the V3 loop and stop the virus from infecting nearby cells, they weren't sure if the antibody would prevent infection by another virus subtype.

The investigators found that the monoclonal antibody was protective and kept those animals receiving it virus-free; however, the researchers detected high viral counts in serum from animals that had not received the virus. Ruprecht says her findings, the first evidence of its kind, won't necessarily result in an HIV vaccine, but they do demonstrate that complete cross-clade protection is possible. Because more than 90 percent of all HIV infections in the world are caused by four clades, such protection would make developing a "universal" vaccine more manageable.

HMS researchers say we are closer to an HIV vaccine than ever before, but caution that we are still years away from an effective vaccine being tested in humans, let alone being on the market. One of the biggest hurdles to vaccine research today is not researchers' understanding of the science of HIV and AIDS, it's dwindling government support for fundamental HIV vaccine research. Desrosiers and others say many good vaccine concepts are going unfunded while many established projects are languishing.

But this hurdle is not deterring scientists, especially those at HMS, who have made such great strides in a relatively short amount of time. Some of their hope comes from history—it took 92 years to develop an effective flu vaccine. "We're climbing a steep hill," says Walker, "but we are making progress."

Scott P. Edwards is a Massachusetts-based science writer.

Smart Tools for Surgery

by Susan Karcz and Ann Marie Menting

Stuck on You

THE LITTLE GREEN LIZARD that hawks insurance may have unusual skills, such as the ability to speak, but a team of HMS and MIT researchers, who have been investigating the capabilities of the gecko, has been inspired by a different attribute—the unique gripping properties of the animal's feet. The team, led by Jeffrey Karp, an HMS assistant professor of medicine at Brigham and Women's Hospital, and Robert Langer, an HMS senior lecturer on surgery and the David H. Koch Institute Professor at MIT, has developed a snug-fitting surgical-grade adhesive bandage that may replace or augment traditional methods of closing surgical wounds, such as with sutures or staples. Karp and his team developed a bandage that meets the requirements for surgical applications—biocompatible, biodegradable, and elastic—by using a biorubber that can conform to the tiny hills and valleys of tissue surfaces.

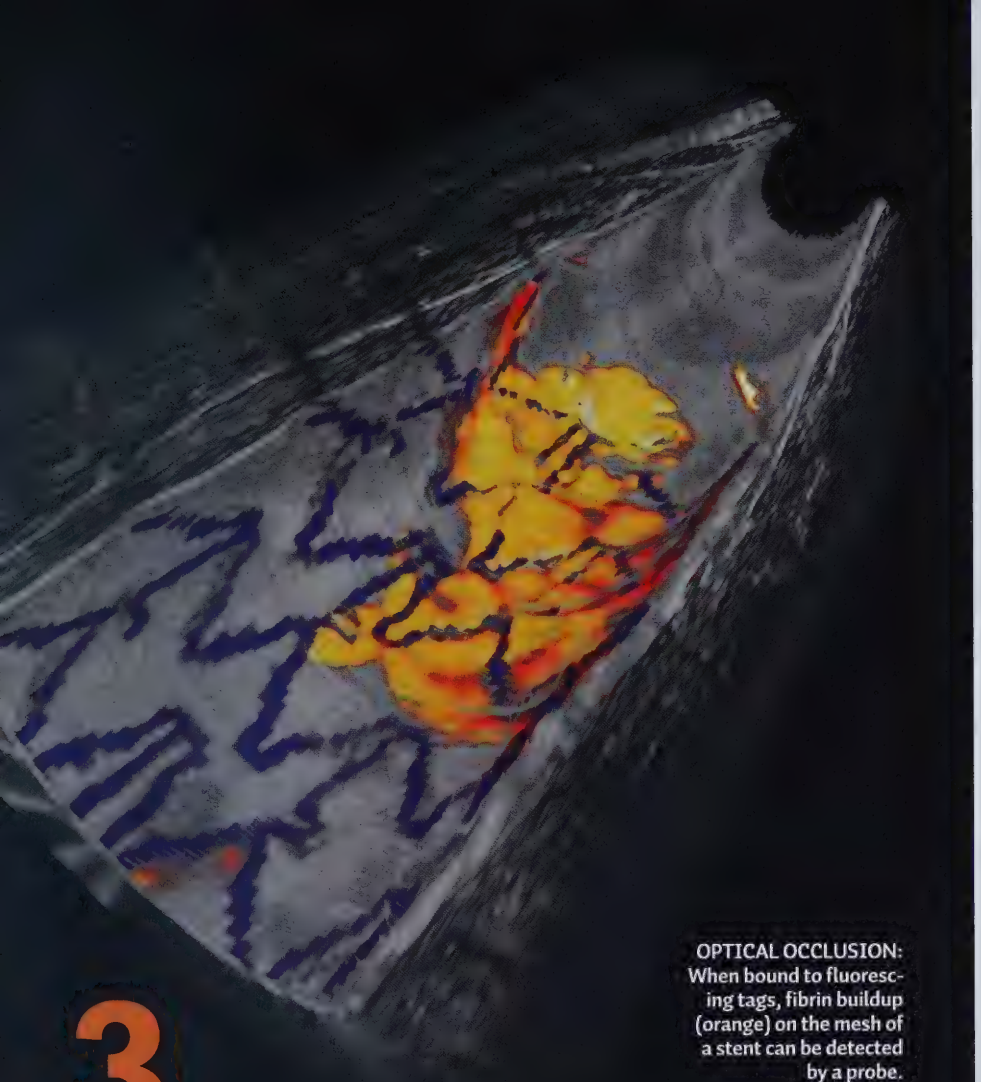
Like the feet of the gecko, which can grip in vertical or inverted positions, this bandage can adhere to uneven surfaces in wet environments, such as human internal organs. Unlike a gecko's grip, this bandage does not need to be removed because it dissolves harmlessly in the body, making it a viable tool for surgical repairs such as patching a hole from a gastric ulcer. The adhesive could even be infused with drugs or growth factors and "tuned" for specific surgical uses. —*SK*

Preserving the Sounds of Music and Words

HOW DO YOU SOLVE A PROBLEM LIKE scarred vocal cords? You call in Steven Zeitels, the Eugene B. Casey Professor of Laryngeal Surgery at HMS and director of the Voice Center at Massachusetts General Hospital. Zeitels's team has developed an innovative polymer gel that mimics the mechanical properties of human vocal cords. This gel, PEG30, has been engineered to match the cords' visco-elasticity and can be injected directly into the damaged area. The gel allows the cords to vibrate normally when air is expelled from the lungs.

Zeitels, along with Robert Langer, an HMS senior lecturer on surgery and the David H. Koch Institute Professor at MIT, and Sandeep Karajanagi, an HMS instructor in surgery at Mass General, tested the synthetic gel in an animal model and found it allowed vibration without causing either local or systemic adverse reactions. This finding holds promise for professional singers like Julie Andrews, whose vocal cords were once damaged. But it is for the millions who lose their voice to diseases such as cancer that the procedure may hold its greatest benefit. It could allow them to recover their normal voices—and sing once more. —*SK*

PHOTOS: COURTESY OF BJØRN CHRISTIAN TØRRISSEN, BJORNFREE.COM (FAR LEFT); COURTESY OF MGH CENTER FOR LARYNGEAL SURGERY AND VOICE REHABILITATION



OPTICAL OCCLUSION: When bound to fluorescing tags, fibrin buildup (orange) on the mesh of a stent can be detected by a probe.

3

A Little Light, Please

WITH ITS ROTATING LASER TIP that snaps and sends detailed images from inside arteries, a new probe developed by Guillermo Tearney '98, an HMS professor of pathology at Massachusetts General Hospital, and Farouc Jaffer, an HMS assistant professor of medicine at the hospital, could provide physicians with news of clot formations in arterial stents well in advance of trouble. The probe, which marries optical frequency domain imaging and near-infrared fluorescence imaging, two microimaging technologies, produces images that show arterial microstructures and provides molecular information on the inner surfaces of arteries, the very surfaces on which troublesome plaques can assemble.

In addition to providing sweeping views of arterial walls, the probe is capable of detecting fluorescing chemical tags that attach preferentially to fibrin. This protein, key to clot formation, can be problematic for people who have had stents surgically inserted to open blocked arteries. Although healthy cells can develop along the stent to help integrate it into the artery, fibrin clots can also develop on unhealed stents—leading to future blockages and risk of heart attack. In an animal model, a stent coated with fluorescent fibrin-rich microthrombi was implanted into the iliac artery and then imaged with the probe. The device successfully detected the fluorescing fibrin.

In future studies of patients with stents, the light-seeking probe could help assess the quality of healing in the stent and the need for anticlotting medications that could avert stent thrombosis, a life-threatening event.

—*AMM*

4

The Beat Goes On

IT WAS A PROBLEM that Pedro del Nido felt compelled to solve. Del Nido, the William Ladd Professor of Child Surgery at HMS and Children's Hospital Boston, knew that performing heart surgery on an infant meant he had to stop the heart. But stilling this organ is a long, invasive procedure that leaves an infant vulnerable to life-threatening complications. So del Nido built tools that would allow cardiac surgeons to operate on tiny hearts while they are beating.

For one of these tools, del Nido used video-game technology to develop an ultrasound imaging system that produces three-dimensional holograms showing the structures inside the beating heart. Another tool, which is being developed with visiting professor Pierre DuPont, is a 3-millimeter–sized device that can enter a heart through the merest whisper of an incision and respond to a joystick control, allowing a surgeon to explore the heart's chambers and to remove blockages, repair faulty valves, and close leaks—all in real time. A third device, called a cardioport, lets surgeons safely introduce instruments into cardiac chambers without worrying about causing blood loss or air embolisms.

Tests in animal models have shown that the imaging system so enhances the surgeon's view of the heart's interior that durations of surgeries can be reduced by nearly half, which could translate to less stress on little hearts.

—*AMM*

BACKSTORY

FROM THE COLLECTIONS AT HARVARD MEDICAL SCHOOL

It is the rare Victorian novel that doesn't include a bedridden or "sickly" person or an infant as part of a plot line. What may be less common, though, is a description of the tools and techniques the caregiver may have used. How would the sick and the small have been sustained?

Today, critically ill people who cannot eat on their own can be nourished by a solution of carbohydrates, amino acids, lipids, and electrolytes delivered by enteral or parenteral feeding. This liquid concoction represents, to the best of modern medicine's knowledge, what the body needs to stay alive. Although the methods for caring for the sick and the vulnerable have changed, the goal has not. As Charles Gatchell, a professor of medicine at the University of Michigan and clinical lecturer at Chicago's Cook County Hospital, wrote in his 1885 book, *How to Feed the Sick*: "the regulation of the diet in disease consists in supplying those foods containing the elements which are lacking in the system, and offering them also in a form to be readily digested and assimilated. Hence, if we can learn the wants of the system, and if we know in what state to introduce the required aliment, we are prepared to intelligently feed the sick." —*Susan Karcz*

PHOTOS: PAUL MORRISON

BEDSIDE MANNERS: The practical requirements of feeding patients and infants blend with the beauty of craftsmanship in these objects from the collections at the Francis A. Countway Library of Medicine. Clockwise, from far left, they include a tonic cup made of quassia wood, a material that imparted medicinal qualities to liquids steeped in it (c. 1850); a porcelain invalid feeding cup (Germany, 1875–1900); a silver pillbox that belonged to John Jeffries (1745–1819), a Boston physician and surgeon; a glass lacteal, or imitation breast (c. 1852), similar to one patented by physician Charles Windship of Roxbury, Massachusetts, in 1841; and a glass infant feeder, believed to be from Pompeii, possibly dating from 79 AD.

Invalid feeding cup, courtesy of the Harvard Medical Library, Francis A. Countway Library of Medicine; all other objects, courtesy of the Boston Medical Library, Francis A. Countway Library of Medicine

FIVE QUESTIONS

FOR TINA YOUNG POUSSAINT

Tina Young Poussaint, MD
Professor of Radiology, Department of Radiology, Children's Hospital Boston

Director of the Neuroimaging Center of the Pediatric Brain Tumor Consortium, Children's Hospital Boston; past president, American Society of Pediatric Neuroradiology.

How did this career path find you?
I attended Mount Holyoke College and participated in the student career exploration project, which for me involved shadowing a pediatrician, and then a pathologist. Both experiences made me realize that I was interested in medicine, although my interest in neuroradiology didn't develop until later, in medical school. I liked the way radiology cut across all specialties, giving me an opportunity to consult with other physicians. That fascination with the inclusive aspect of radiology has stayed with me and has helped shape my career.

In what ways has the idea of collaboration shaped things for you?
Well, if you like collaboration, Children's is a great place to work. And a spirit of collaboration is at the heart of the Neuroimaging Center of the Pediatric Brain Tumor Consortium. This 11-hospital consortium focuses on the study of tumor biology and new therapies for primary central nervous system tumors of childhood. I am so proud of being named the director and principal investigator of the Center.

What technical innovations have changed your field since you started your career?
When I first started, most imaging involved ultrasound and CT scans. I was in my early residency when MR imaging arrived—that gave us an opportunity to better visualize the structural anatomy of the brain. Now, with MR diffusion, we can actually see evidence of an acute stroke. Two other great new techniques are MR profusion, which shows blood flow and volume in the brain, and functional MRI, which highlights changes in the blood that reflect the neural activity within the brain. And then there's molecular imaging, which can show cellular structures within the brain. So the technology has evolved from allowing only anatomic descriptions to imaging physiological processes.

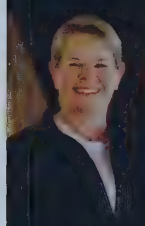
What issues related to pediatric neuroimaging are you working on?
There's an ongoing effort to raise awareness about ways to protect children against overexposure to radiation from imaging. This is a serious issue; developing children are potentially at risk from cumulative amounts of radiation from CT scanning. One effort at education, the Image Gently campaign, is an international program of the Alliance for Radiation Safety in Pediatric Imaging. The kinds of questions we want physicians to ask are basic, for example: Does the image have to be the best one possible, or can a little image resolution be sacrificed for a lower radiation dose? At Children's, checks like these have reduced the number of CTs in our department.

What inspires you and motivates you to seek new challenges?
There's a quotation from Harriet Tubman, the great African American abolitionist—and spy!—that begins, "Every great dream begins with a dreamer." I believe that and have tried to make it a part of my life, including my professional life. I'm not afraid to explore new ideas, including my own. I may not know exactly how an idea's going to materialize, but I frame it by focusing on excellence and on trying to help and serve others. By focusing on those things, I maintain my momentum, and remain inspired.

—Susan Karcz

PHOTO: JOHN SOARES

President's Report



This year's Alumni Council got off to a great start with the October meeting. In addition to updates on the School from Dean Jeffrey Flier, including information on the new Center for Primary Care and the new Initiative in Systems Pharmacology, we had lively discussions around the Council's role in the coming years. Two areas of interest emerged, the first concrete and the second abstract.

First, we are going to address the issue of presentation of class notes, which are currently published three times a year in *Harvard Medicine*. The Council believes that new approaches that span generations and use multiple technologies should be implemented. We will survey the broader alumni group for ideas.

Second, we want to address continuity of idealism, professionalism, and curiosity as students move through their clinical years. The Council will conduct a strategic planning session before the fiscal year's end to begin to refine these concepts. All thoughts are welcome.

Phyllis Gardner '76 is a professor of medicine at Stanford University School of Medicine and a partner at Essex Woodlands.

EXPRESS YOURSELF: Annual workshop for health care professionals aims to bring out the writer within the white coat.

BEYOND PRESCRIPTION

Gaining the courage to put pen to paper

A doctor steps to the podium, notes in hand, and looks awkwardly across a ballroom of peers. She waits as the judges evaluate the previous presentation. Seconds tick by, the room heavy with the sounds of shifting chairs and clearing throats.

"On your mark, get set, go!" says the moderator as she winds the timer.

The doctor has 90 seconds to excite the room. In just over a minute, she must introduce herself, her idea, and her plan. She must convince a panel of literary agents, editors, and publishers, along with a roomful of potential readers, not only that she has a great book idea, but also that she is the perfect person to write—ding!—it.

Each spring, a cadre of would-be and already-are authors gathers in Copley Square for "Improving Healthcare Leadership, Communication and Outcomes through Writing and Publishing," a course offered by Harvard Medical School's Department of Continuing Education. The course, the brainchild of Julie Silver, an HMS assistant professor of physical medicine and rehabilitation at Spaulding Rehabilitation Hospital and a prolific author herself, covers all things important to an author, from platform and proposal to publishing and publicity. While the primary intent is to educate doctors interested in publishing, the course is also open to other health care professionals.

According to Jeff Brown, an HMS clinical instructor in psychology at McLean Hospital and co-author of *The Winner's Brain* (Da Capo Press, 2010), the secrets of successful authors are not unlike those of successful marathoners. Both self-talk their way to the finish. Both practice. And both keep an eye on their goal while enjoying the hard work it takes to reach it.

For many attendees, the course sparks creativity. While several authors pitched books about innovative medical ideas, leadership advice, and self-help book ideas, others pitched memoirs, fiction, and even performance art. It was clear that every author had spent a great deal of time preparing.

Preparation, says Brown, is, in fact, key to being a successful author. Beyond preparing the pitch, authors must develop their online presence, their reputation, their data, and their writing skills. "This course is about helping people find success as they define it," Brown adds.

"Doctors need to be great communicators," says Silver. "Writing and publishing are powerful ways for doctors to influence health care and to convey health information beyond their own patients."

Interested in some guidance as you take pen in hand? To learn more about the course, visit www.harvardwriters.org.

—Elizabeth Dougherty

PHOTOS: GARY PARKER (ABOVE LEFT); COURTESY OF LIZA GREEN

CLASS NOTES

NEWS FROM ALUMNI

1942

J. Bradford Millet

"Still playing golf twice a week, and going to local medical meetings. Winning at bridge and poker."

1945

John Packard

"2011 has been a tough year. My son Charles, age 53, died of a heart attack in February, and Ann, my wife of almost 67 years, died on Easter Sunday of Alzheimer's. I am getting lots of support from our seven surviving children."

1950

Kenneth Walker

"I attended the funeral of **Avard Mitchell**, the last member of my cadaver group. It was good to see **Don Gair** at that time."

1954

William Lassiter

"I'm sorry to report that in May, Diane, my wife and constant companion for 55 years, died suddenly of cardiopulmonary failure."

J. Donald Ostrow

"Judy and I recently completed a trip through central Europe, including a cruise on the Elbe River and three days each in Prague and Berlin. Most impressive was Dresden, which had been destroyed by fire-bombing in 1944, but has been restored in the 20 years since Germany reunified."

1955

David G. Nathan

was presented in December with the 2011 Wallace H. Coulter Award for Lifetime Achievement in Hematology, the highest honor of the American Society of Hematology.

1956

Robert Chamberlin

"Still alive! I'm working with a local United Way house to develop a resource center for families with young children, and playing the recorder with an English country dance band here in Fort Myers, Florida."

1957

John Retzlaff

"My wife, Tommi, and I are enjoying good health and a busy retirement. We traveled to Germany in September, where I gave an honorary presentation at the meeting of the Intraocular Lens Power Club."

1960

Mark Perlroth

"The blessing of grandchildren has been sorely tested by housing three (with parents), while their house underwent a three-month remodel. Otherwise, life is okay. No health problems, and retirement allows travel to Australia and Europe. But I miss the social and intellectual environment of the past 40 years."

1963

John Mendelsohn

has been named the L.E. and Virginia Simmons Senior Fellow in Health and Technology Policy at Rice University's James A. Baker III Institute for Public Policy.

1965

Joseph Lane

was honored with a Lifetime Achievement Award by the Hospital for Special Surgery in New York City, for his work in metabolic bone disease.

1968

Robert Rutherford

"Moved to California after 20 years in Key West. I tried retirement, back fusion, and hip replacements, and I'm back to work three days a week in the local community clinic. Wonderful wife, K.T., great friends, and a great place. Our garden flourishes. Life is truly good."

1971

Donald Burke

has been named a Distinguished University Professor of Health Science and Policy at the University of Pittsburgh.

PHOTOS: JOSHUA TOUSTER

1972

Edward J. Benz, Jr.
was appointed to the Board of Directors of the Massachusetts Life Sciences Center in Waltham, Massachusetts, by Governor Deval Patrick.

1973

Elizabeth Rappaport
"We are enjoying our grandson, Gabriel, now two years old. His mom, our daughter Miriam, received her EdD from the University of Pennsylvania. **Noah Harris** and **Barbara Abercrombie '75** joined us for the celebration."

1974

C. Alan Brown
received the Bronze Star for meritorious service as battalion surgeon for the 4th Light Armored Reconnaissance Battalion, USMC. "I deployed to Helmand Province, Afghanistan, serving as medical officer from October 2009 to June 2010. My corpsmen and I were responsible for providing medical care to the Marines and to the local Afghan villagers. I have since returned to my practice of clinical and interventional cardiology with the Santa Barbara Cardiovascular Medical Group."

1975

Jessie Sherrod
"I am now a retired pediatric infectious disease specialist and hospital epidemiologist. Earlier this year, I was a recipient of the Women of the Year Awards conferred by the Los Angeles County Commission for Women. In 1982, I founded the Association of Black Women Physicians of Southern California. In 2002, I was among the first African Americans in the initial group of inductees into the UCLA School of Public Health Alumni Hall of Fame for outstanding service in public health. In 1992, I was inducted into the Tougaloo College Hall of Fame in medicine."

Robert Weinreb
has been named chair of the Department of Ophthalmology and director of the Shiley Eye Center at the University of California San Diego School of Medicine.

1976

Laurie Glimcher
has been named dean of Weill Cornell Medical College, effective January 1, 2012.

1978

Katherine Murray-Leisure
"I closed my private practice of 25 years in October 2010, and moved to the southeast coast of Massachusetts to start an internal medicine, infectious diseases, and travel service. With my two children launched and independent, I was free to move back to family and friends, and to enjoy this oceanside community. Windsurfing and running with my dog on Sagamore Beach and the Cape Cod Canal has been fabulous fun."

1979

Charles R. Bridges, Jr.
has been selected to chair the Department of Thoracic and Cardiovascular Surgery at Carolinas Medical Center in Charlotte, North Carolina.

1980

Mark Goldberg
has been appointed senior vice president of product development at Synageva BioPharma Corporation, in Lexington, Massachusetts.

1981

Robert Sackstein
and his laboratory at Brigham and Women's Hospital accepted a $17 million Program of Excellence Award from the National Institutes of Health.

1983

Jonathan Bromberg
has been appointed head of the Division of Transplantation in the Department of Surgery at the University of Maryland School of Medicine.

CLASS NOTES

NEWS FROM ALUMNI

1985

Lynt B. Johnson
has been named the Robert J. Coffey Professor and Chairman of the Department of Surgery at Georgetown University Hospital in Washington, DC.

Regis O'Keefe
has been appointed to the National Institutes of Health Council of Councils.

1987

Emery Brown
has received the 2011 Jerome Sacks Award from the National Institute of Statistical Sciences in Research Triangle Park, North Carolina, for cross-disciplinary research.

Cato Laurencin
has stepped down as dean of the University of Connecticut Medical School and as vice president of the UConn Health Center.

Valerie Montgomery Rice
received the 2011 Multicultural Women's Legacy Award from Working Mother Media. She was honored at the 9th Annual Best Companies for Multicultural Women National Conference in New York City.

1990

Paul Farmer
was selected by the Secretary-General of the United Nations for special recognition on World Humanitarian Day in August. Farmer was also presented with the 2011 Pro Bono Humanum Award by the Prix Galien USA Committee at an event in New York City in September.

Nicole Glaser
has been named to the Dean's Professorship in Childhood Diabetes Research at the University of California Davis School of Medicine.

Christopher Senkowski
was nominated by the American College of Surgeons to serve on an Agency for Healthcare Research and Quality clinical-expert panel to evaluate surgical clinical measures to improve quality of care at hospitals nationwide.

1991

George Q. Daley
was honored by the American Society of Hematology with the 2011 E. Donnall Thomas Lecture and Prize. Daley presented his lecture at the ASH Annual Meeting in San Diego in December.

Sam Hwang
has been named the first Thomas J. Russell Family/Milwaukee Community Dermatologists Chair of Dermatology at The Medical College of Wisconsin.

1996

B. Price Kerfoot
was one of four Harvard faculty members, and the only HMS alumnus, to receive a 2011 Presidential Early Career Award for Scientists and Engineers from President Barack Obama.

1998

Jeremy Cannon
"I received the 2011 Paul W. Myers award as the top physician in the U.S. Air Force at a ceremony in Washington, DC, in September. I very much credit my HMS mentors for this and all of the work I have been able to do as a surgeon in the Air Force during these historic times."

1999

Charles Fox
"I was named to *Atlanta* magazine's 2011 list of top doctors in the field of gastroenterology. This honor is based on a survey of local physicians and is published every year. I know that I could never have achieved this kind of success, respect, and recognition without the education and experience I received at HMS."

2000

Glenda Callender
"I joined the faculty of the University of Louisville (Kentucky) in October 2010 as an assistant professor of surgery. My clinical focus is endocrine surgery and surgical oncology. My husband, Jeff Roszkowski, has made a recent career change and is currently enjoying culinary school!"

2009

Elizabeth Ann Côté
has been selected to the 2011-2012 class of White House Fellows. This program offers exceptional young men and women first-hand experience working at the highest levels of the federal government.

PHOTO: JOSHUA TOUSTER

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1935

John Judd Shields

Died on July 6, 2011, at the age of 100, at his home in Rydal, Pennsylvania. Shields served in the Aleutians during World War II, and returned to practice pediatrics in the Philadelphia area. His solo practice grew into Abington Pediatric Associates in Abington, Pennsylvania. He became chief of the pediatric service at Germantown Hospital in Philadelphia, and chief of pediatrics at Abington Memorial Hospital, where he served on staff for 38 years. Shields was predeceased by his wife, Julia (Judy), and daughter, Susan Howorth. He is survived by his sons, James and Thomas, six grandchildren, and eleven great-grandchildren.

1940

Malcolm W. Bick

Died on June 4, 2011, at the age of 95, in Nokomis, Florida. Bick served as a battalion surgeon and captain in the U.S. Army during World War II, and earned a Purple Heart and the Meritorious Service Award. He maintained an ophthalmology practice in Springfield and Northampton, Massachusetts, for 35 years, and was chief ophthalmologist at Wesson Memorial Hospital in Springfield, and Cooley Dickinson Hospital in Northampton. He was elected Life Fellow of the American Academy of Ophthalmology. Bick was predeceased by his daughter, Elizabeth Lonsdorf. He is survived by his wife of 71 years, Esther; son, Michael; daughter, Katherine; four grandchildren; one step-grandson; and five great-grandchildren.

1943

Richard Eckhardt

Died on July 27, 2011, at the age of 93, in Amana, Iowa. Eckhardt served in the U.S. Navy during the Korean War. He served as chief of the medical service and as chief of staff at the Iowa City VA Hospital, and on the faculty of the Department of Internal Medicine at the University of Iowa College of Medicine, from which he retired as full professor. In 1968, he was appointed associate dean for VA Hospital Affairs. Eckhardt was predeceased by his youngest daughter, Barbara. He is survived by his wife, Catherine; three daughters, Dale, Catherine Bartholow, and Jane McMullen; six grandchildren; and three great-grandchildren.

1944

Charles Davenport Cook

Died on September 4, 2011, at the age of 91. Cook served as a physician in the U.S. Army in post-World War II Germany. He was chief of the pediatrics department at Yale University School of Medicine from 1964 to 1972; SUNY Downstate Medical Center in Brooklyn, New York; and Rochester General Hospital, New York. He founded the Hill Health Center in New Haven, Connecticut. Cook is survived by his wife, Carolyn; five children; two stepchildren; thirteen grandchildren; and five great-grandchildren.

William W. Faloon

Died on June 23, 2011, at the age of 90, in Pittsford, New York. Following faculty appointments at Albany Medical School and Upstate Medical Center in Syracuse, New York, Faloon was appointed professor of medicine at the University of Rochester School of Medicine and Dentistry in 1968, and became professor emeritus in 1992. He served as chief of medicine at the Highland Hospital in Rochester, New York, and as its director of gastroenterology and nutrition. He is survived by his wife of 62 years, Roberta; children, Karen Durham, William, Jr., and Nancy Dodd; four grandchildren, and one great-grandchild.

Edmund C. Meadows

Died on July 26, 2011, at the age of 90, in Bennington, Vermont. Meadows served as an officer in the U.S. Navy during World War II and the Korean War. He was chief of surgery at Leominster Hospital in Massachusetts from 1954 until his retirement in 1986. Meadows is survived by his three daughters, Lois Dorman, Melinda Miller, and Sarah; two sons, Edmund and Jim; seven grandchildren; and six great-grandchildren.

D. Ralph Millard

Died on June 19, 2011, at the age of 92, of heart failure, at his home in Sunny Isles Beach, Florida. Millard served in the U.S. Navy during World War II, and was a chief plastic surgeon for the U.S. Marine Corps during the Korean War. He was a pioneer in plastic surgery, and, in the 1950s, developed a technique known as rotation advancement, used to correct cleft lips in children. He was chair of the plastic surgery division at what is now the University of Miami Miller School of Medicine, and served as plastic surgery chief at Jackson Memorial Hospital in Miami. He received the American Society of Plastic and Reconstructive Surgeons' highest award in 1988, and was honored with a bronze bust by the Miami Children's Hospital International Hall of Fame in 1991. Millard was predeceased by his wife of 45 years, Barbara. He is survived by his daughter, Meleney Moore; sons, Bond and Duke; and six grandchildren.

1945

Lester H. Tobin

Died on July 1, 2011, one month before the death of his wife, Phyllis. He is survived by his daughters, Elizabeth Brager and Carol Haskin; sons, Eric and Michael; ten grandchildren; and several great-grandchildren.

1947

Alexander Blum, Jr.

Died on August 2, 2011, at the age of 87, of complications from heart disease. Blum served in the U.S. Naval Reserve, and was called to active duty in 1950. He served overseas in Japan and Korea as a medical officer for an artillery battalion, and was awarded the Bronze Star and Distinguished Unit Citation for his work in Korea. He was a founding member of the Mt. Kisco Medical Group, with a practice at Northern Westchester Hospital in Mt. Kisco, New York. He was also an attending pediatrician in pediatric endocrinology at Columbia Presbyterian Medical Center in New York City. Blum is survived by his wife of 61 years, Linda; two daughters, Jill Millis and Lisa Donegan; son, Geoffrey; and eight grandchildren.

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

Paul William Braunstein

Died on June 18, 2011, at the age of 86, at his home in Jamesville, New York. Braunstein served as a surgeon in U.S. naval hospitals in Japan and Annapolis, Maryland, during the Korean War. He was a general surgeon and director of surgery at Southside Hospital in Bay Shore, New York, and a two-term governor of the American College of Surgeons. Braunstein is survived by his wife of 62 years, Barbara; eight daughters, Claire Gunnels, Barbara Wilson, Janet Moody, Martha, Laura White, Julia Dailey, Carrie D'Angelo, and Emily Nazarian; four sons, Paul, Glenn, Mark, and James; forty-three grandchildren; and one great-grandchild.

Weldon H. Jordan

Died on July 13, 2011, at the age of 87. Jordan served in the U.S. Army's 24th Division in Korea. He began an internal medicine practice in Fayetteville, North Carolina, in 1954, and was a visiting clinical professor of medicine at the University of North Carolina School of Medicine from 1958 to 1989. He became chief of staff at Cape Fear Valley Medical Center and Highsmith Rainey Hospital in Fayetteville. Jordan is survived by his wife of 58 years, Mary Lynn; and sons, Weldon, Jr., Richard, Stuart, and Peter.

1949

John F. Morrissey

Died on June 14, 2011, at his home in Bend, Oregon. Morrissey spent his entire career at the University of Wisconsin at Madison, serving as vice-chairman of the Department of Medicine from 1973 to 1984, and retiring as an emeritus professor of medicine in 1989. He pioneered the use of the gastric camera and established the first endoscopic training program in the United States. In 1983, he received the Rudolph Schindler Award from the American Society of Gastrointestinal Endoscopy. Morrissey was predeceased by his first wife, Ruth. He is survived by his second wife, Shirley; his daughters, Ann and Sara; and two grandchildren.

Correction

The obituaries of the following five members of HMS class of 1949 were incorrectly listed under class year 1948 in the Summer issue: Joseph Claude Finney, James Basil Gabriel, John "Jack" Reardan, Peter G. Robbins, and Charles Howard Wells. The editors regret the error.

1951

Elizabeth H. Sult

Died on June 3, 2011, at the age of 86. Sult was a pediatrician in Roseburg, Oregon, for many years. She and her husband, Francis, served as medical missionaries in Zaire from 1977 to 1984, and then moved to Salem, Oregon. Sult is survived by her husband; their daughters, Heidi Thomas, Susan, Lori Goree, and Terri; and eight grandchildren.

1952

Richard B. Kearsley

Died on July 1, 2011. Kearsley served in the U.S. Army during World War II. He maintained a pediatrics practice in Norwell, Massachusetts, and co-authored *Infancy: Its Place in Human Development*. Kearsley was predeceased by his first wife, Nancy. He is survived by his second wife, Carmella; his children, Richard, Jr., Ann, Michael, Jeanne, and Martha; and five grandchildren.

1953

Roy William Chesnut, Jr.

Died on August 27, 2011, at the age of 85, in Dickeyville, Maryland. Chesnut served in the U.S. Navy, on the aircraft carrier USS *Tarawa*, during World War II. He trained in internal medicine and cardiology, and was on staff at the former Veterans Hospital in Perryville, Maryland, after heading the student health service at Johns Hopkins University for many years. Chesnut was predeceased by his brother, Walter G. Chesnut. He is survived by his sister, Ann C. Galt; longtime friend, Donald W. Alexander; and eight nieces and nephews.

1957

William Henry Cox

Died on August 16, 2011, at the age of 79, at his home in Big Spring, Texas. Cox maintained a family practice in Basking Ridge, New Jersey, for many years, and later returned to his native Texas to work at the VA Medical Center in Big Spring. He is survived by his daughters, Kathleen Chang and Linda MacDonald; sons, Jeff, Steven, David, and Thomas; and seven grandchildren.

Ralph P. Engle, Jr.

Died on June 21, 2011, at the age of 79, at his home in Chestnut Hill, Massachusetts. Engle had a long and distinguished career as a psy-

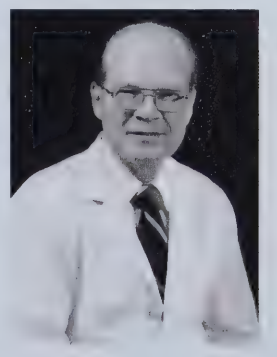


PHOTO: COURTESY OF MASSACHUSETTS GENERAL HOSPITAL

George Shattuck Richardson 1921–2011

George S. Richardson '46, distinguished editor of the *Harvard Medical Alumni Bulletin* from 1971–1980, died on July 1, 2011, at his home in Nahant, Massachusetts. The youngest of three brothers, Richardson was born into a storied family of physicians: his father, both grandfathers, a great-, and a great-great-grandfather were chiefs of surgery or medicine and professors at Massachusetts General Hospital, where Richardson himself served as a gynecologic surgeon for more than five decades. Richardson joined Mass General in 1955 as a staff member of Vincent Memorial Hospital. At Vincent, Richardson dedicated his career to researching and performing surgery on various cancers of the reproductive system. He was acting chief of the Vincent from 1985 to 1988, and retired from Mass General in 1995.

The love of words that Richardson displayed as *Bulletin* editor remained strong throughout his life, leading to an appointment as book review editor of the *New England Journal of Medicine*, a chairmanship of Mass General's Treadwell Library committee, and in the past several decades, to his becoming a published poet. Richardson is survived by his wife of 54 years, Rebekah; his sons, Jonathan, William, and Frederick; and three grandchildren.

choanalyst. He was predeceased by his wife, Corliss. He is survived by his sons, Ralph III and Arthur; and six grandchildren.

1960

Fritz H. Bach

Died on August 14, 2011, of cardiac arrest, at the age of 77, at his home in Manchester-by-the-Sea, Massachusetts. In 1938, Bach and his brother fled Vienna after Kristallnacht and sought refuge in England. With the sponsorship of a U.S. soldier, his family emigrated to the U.S. and settled in Burlington, Vermont. Bach was a pioneer in developing techniques that prevent tissue rejection following organ and bone marrow transplantation. He taught and did research at the University of Wisconsin at Madison, the University of Minnesota at Minneapolis, and Columbia and Harvard Medical Schools. Bach was an emeritus professor of surgery at HMS and was named Lewis Thomas Distinguished Professor of Surgery in 2003. Bach is survived by his children, **David '87,** Peter, Wendy, Kathryn, Erika, and Dana; and four grandchildren.

1961

William Zachary Yahr

Died on September 15, 2011, of brain cancer, at his home in Miami Shores, Florida. A pioneer in several aspects of heart surgery, Yahr helped develop the intra-aortic balloon pump and patented an ambidextrous clamp. In the 1970s he moved from New York to Miami Beach, where he served as vice-chairman of the Department of Thoracic and Cardiovascular Surgery at Mount Sinai Hospital. Yahr is survived by his daughters, Elizabeth Southard and Harriette; son, Alexander; and two grandchildren.

1963

David D. Swenson

Died on July 28, 2011, at the age of 76, in New Bedford, Massachusetts. Swenson served as senior assistant surgeon for the Public Health Services in Virginia and eventually earned the rank of captain. He was a forensic psychiatrist for the Commonwealth of Massachusetts in Essex County for 30 years. Swenson is survived by his wife, Janice; daughters, Karen Pickell, Gretchen, and Deborah Silva; and ten grandchildren.

1964

William C. Sheehan

Died on July 11, 2011, at the age of 71, of Parkinson's disease. Sheehan practiced general medicine at Sansum Clinic in Santa Barbara, California, and then returned to his native New England to treat pulmonary diseases. In 1976, he joined the Truesdale Clinic in Fall River, Massachusetts, and later founded a pulmonary care clinic there. Sheehan is survived by his wife, Ann; daughters, Alexandra Hartmann, Erika, and Natalie Dias; and fourteen grandchildren.

1965

Mark A. Lawrence

Died on July 22, 2011, at the age of 71, at his home in McLean, Virginia. Lawrence served on the psychiatric faculties of Georgetown University Medical School and St. Elizabeth's Hospital in Washington, DC. In 1984, he cofounded the Center for Healing and Imagery in Washington, DC. Lawrence mentored hundreds of therapists in the McLean area, and was a valued sounding board on difficult cases. Lawrence is survived by his wife, Karen; daughter, Katherine; and one grandchild.

1968

Ralph M. Steinman

Died on September 30, 2011, at the age of 68, of pancreatic cancer. Steinman was a co-recipient of the 2011 Nobel Prize in Medicine or Physiology, which was announced three days after his death. Although Nobel Prizes are not awarded posthumously, the Nobel Committee decided to allow the award to stand. Steinman and Zanvil Cohn discovered a new class of cells—dendritic cells—in 1973, laying the foundation for many important discoveries in immunology. His subsequent research revealed the role of dendritic cells as key mediators in several immune responses, including graft rejection, resistance to tumors, and autoimmune diseases. Steinman was the Henry G. Kunkel Professor and director of the Christopher H. Browne Center for Immunology and Immune Diseases at Rockefeller University. Steinman is survived by his wife, Claudia; his daughters, Lesley and Alexis; son, Adam; and three grandchildren.

1969

Bernadine P. Healy

Died on August 6, 2011, at the age of 67, of brain cancer, at her home in Gates Mills, Ohio. Healy was the first woman to head the National Institutes of Health and the first physician to head the American Red Cross. She was a professor at Johns Hopkins University, dean of the Ohio State University Medical School, a science advisor to the White House, and president of the American Heart Association. At NIH in the early 1990s, Healy was instrumental in overturning the conventional wisdom on women's health, changing, for example, the perception that heart disease is primarily a men's health issue. She began the Women's Health Initiative, a landmark study on cardiovascular disease, osteoporosis, and cancer in middle-aged and older women. Healy is survived by her husband, Floyd Loop; and daughters, Bartlett Bulkley and Marie McGrath Loop.

1973

Christian R. Raetz

Died on August 16, 2011. Raetz joined the biochemistry department at the University of Wisconsin at Madison in 1976, and was executive director of basic research, biochemistry, and microbiology at Merck Research Laboratories. He served as biochemistry chair at Duke University from 1993 to 2007, and was elected to the National Academy of Sciences in 2006. Raetz is survived by his wife, Madeline; daughters, Jackie and Lizzie; and one grandson.

TAKING A HISTORY

PROFILE OF MARGARET HAMBURG

SAFETY CAP: Margaret Hamburg helps protect public health by overseeing the quality of the nation's food and drugs.

CLAIMS TO FAME: Commissioner of the Food and Drug Administration, former New York City Health Commissioner, former Assistant Secretary for Planning and Evaluation in the U.S. Department of Health and Human Services, and an expert in community health and in biodefense.

GROWING UP MEDICAL: The daughter of prominent psychiatrists and public intellectuals, Margaret Hamburg '83 seemed destined for a career in academic medicine. But her course changed when a residency and a fellowship in New York City coincided with an emerging public health crisis: HIV and AIDS. "Even as we learned more about the disease, we were hampered in what we could effectively do to address it," Hamburg says. "And that made me want to learn more about health policy and public health."

CHARTING A COURSE: She had some catching up to do. "In med school, my greatest exposure to public health was eating in the cafeteria at the School of Public Health," Hamburg says. So she made her way to the U.S. Office of Disease Prevention and Health Promotion. "I thought I would go for a couple years and just get exposed," she says. "But I became immersed." By 1989, Hamburg was assistant director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, where she studied HIV and AIDS. Within two years, during the worst of the U.S. AIDS epidemic, Hamburg was tapped to lead New York City's Department of Health.

CITY LIGHTS: "It was enormously challenging and rewarding, and has shaped all my subsequent efforts," she says of her time in New York City. AIDS and other public health problems, including tuberculosis, intertwined with a thicket of social factors, from housing and homelessness to incarceration and drug addiction. But Hamburg refused to surrender to complexity. The key, she says, was "taking a stepwise and science-based approach to the problems before us."

TOOLS OF THE TRADE: At the FDA, where public demands for safety and innovation sometimes compete, Hamburg has advocated for investment in regulatory science as an answer to both. "Regulatory science is the ultimate bridge from a promising discovery to a real-world medical intervention. Yet much of the investment in science has neglected it."

GREAT EXPECTATIONS: Despite her achievements, Hamburg's career path hasn't pleased everyone. "My great-aunt Winnie was very excited that I was going to become a doctor," Hamburg says. "She said, 'Now you can marry a doctor.' Later, when I became health commissioner, she complained to my father that I was giving up my career as 'a real doctor.'"

—R. Alan Leo

PHOTO: MARK FINKENSTAEDT

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